Review Article

*Int J. Pharm. Drug. Anal, Vol: 12, Issue: 2, 2024; 38-47*

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.org ISSN: 2348:8948

# MENSTRUAL CYCLE DISORDERS: A CORRELATION WITH GENETIC ALTERATIONS

**Shrishti Mishra [1], Arti Verma[1], Archita Tiwari [2], Bharat Mishra [3]**

[1]RGS College of Pharmacy, Itaunja, Lucknow

[2]Faculty of Pharmacy, Khwaja Moinuddin Chishti Language University, Lucknow

[3]Institute of Pharmacy, Dr. Shakuntala Misra National Rehabilitation University, Lucknow

*Received: 18 Apr 2024 Revised: 26 Apr 2024 Accepted: 04 June 2024*

**Abstract**

The menstrual cycle is considered the fifth vital sign among women. The pituitary, thyroid, pancreas, adrenal, and ovaries are endocrine glands that play a crucial role in governing the menstrual cycle. Endocrine ailments trigger periods of menstruation disturbances throughout a woman's reproductive life. The duration and volume of menstrual bleeding can serve as indicators of endocrine problems. Oligomenorrhea, which refers to monthly periods longer than 35 days, is the most prevalent menstrual disruption observed in endocrine illnesses such as thyrotoxicosis, hypothyroidism, polycystic ovarian syndrome, Cushing's syndrome, and diabetes, based on the existing evidence. The intricate endocrine pathways are crucial in regulating a woman's menstrual cycle.. Menstrual Irregularities are caused due to eating disorders, extreme weight loss or too much exercising, Polycystic ovary syndrome (PCOS), Premature ovarian failure, Pelvic inflammatory disease (PID) and Pregnancy or breast-feeding. Mensesare affected by various factors like junk food, obesity, skipping breakfast lack of physical activity etc. PCOS, Diabetes, Hyperprolactinemia, Hypothyroidism, Thyrotoxicosis, and Cushing's syndrome are some menstrual disorders which occur due to genetic alterations. All these disorders can be primarily treated by Nutritional Considerations and herbal treatments. In order to achieve a regular menstrual cycle and overcome these diseases, nutritional supplements and lifestyle modifications must be prioritized.

**Keywords:** Menstrual irregularities, PCOS, obesity, Genetic alterations



***Corresponding Author**

Prof. Dr. Bharat Mishra

Institute of Pharmacy,

Dr. Shakuntala Misra National Rehabilitation University, Lucknow

DOI: https://doi.org/10.47957/ijpda.v12i2.596

**Produced and Published by**

South Asian Academic Publications

## Introduction

The menstrual cycle is contemplatedas the fifth core sign among women. The pituitary gland, thyroid gland, pancreas, adrenal glands, and ovaries are all parts of the endocrine system that play a significant part in the control of menstrual cycles. Throughout the course of a woman's reproductive life, those who suffer from endocrine problems are more likely to have menstrual misery. Oligomenorrhea, which is defined as cycles that last for more than 35 days, is the most prevalent type of menstrual misery and is associated with endocrine problems such as thyrotoxicosis, hypothyroidism, polycystic ovarian syndrome, Cushing's syndrome, and diabetes. Complex endocrine pathways play an important part in the menstrual cycle of a woman. These pathways are also influenced by the length and volume of bleeding, both of which can be indicators of endocrine abnormalities. It is the cyclic response to the hormone production from the hypothalamus, pituitary, and ovaries (HPO) axis that is responsible for the phenomenon known as the monthly cycle [1].

The hormone system plays animportant role in the regularity of the menstrual calendar setting. Menstrual disorders are one of the most common gynaecological complaints of women, a common trouble that continues from menarche to menopause [2].

Pathophysiological disturbancesoccur due to genetic variance, epigenetic changes, and disquiet lifestyle, which may lead to hyperandrogenism, insulin resistance, and chronic inflammation in PCOS females. Menstrual disease progression involves various proteins and signaling cascades at the molecular level, resulting in the inadequacy of a single genetic diagnostic method. The

genetic progression of PCOS, POI, and other menstrual illnesses is contingent upon individual genes, gene-gene interactions, and the modified environmental conditions of genes. Identifying the variant critical gene that alters its expression and sequence to influence protein function is crucial for determining the genetic composition of menstruation diseases [3].

It has long been known that chromosomal mutations are the root cause of erratic periods, infertility, recurrent premature deliveries, erroneous sexual development, and premature ovarian insufficiency (POI) [2].

Menstruation issues can be detected through genetic research as their underlying cause. The context of diagnosis and therapy for many reproductive and metabolic conditions has transformed as a result of genome-wide association studies (GWAS) and associated genetic research [4].

Over the past few years, numerous genetic loci have been discovered, and these loci have the potential to be incorporated into the diagnosis, prediction, and treatment of diseases. Additionally, the World Health Organization (WHO) has the ability to categorize menstrual cycle disorders as either originating from secondary sources or as an original condition of the ovaries: Primary ovarian insufficiency, also known as hypergonadotrophic hypogonadism, is characterized by the inability of the ovary to respond appropriately to gonadotropin stimulation from the pituitary gland and the cognitive system. Secondary ovarian insufficiency, also known as hypogonadotrophic hypogonadism, is characterized by an inadequate quantity of gonadotropin stimulation being generated by the brain and the adrenal gland [5].

Causes of Menstrual Irregularities: Eating disorders, such as anorexia nervosa, as well as significant weight reduction and increased physical activity, can disrupt menstrual cycles. The elevated production of androgen causes hyperinsulinemia insulin resistance and obesity.It has been established that PCOS is commonly associated with dysfunctional granulosa cells (GCs), which exhibit inadequate apoptosis and excessive proliferation. Abnormalities in the GC may be caused by elevated levels of circulating insulin. Specifically, this insulin can promote the overexpression of mir-93 and the downregulation of mir-145, which in turn promote cell proliferation and block apoptosis. PCOS women have higher levels of androgens, w-hich causes the mitochondria in various bodily tissues to over-activate, favouring an excess of ATP. An overabundance of ATP molecules inhibits the AMPK signalling pathway in insulin-sensitive tissues, resulting in hyperinsulinemia and insulin resistance in pancreatic β-cells and α-cells.Insulin and insulin growth factor 1 (IGF-1) causes the inner theca cells to undergo certain physiological changes that lead to hypertrophy and an excess of androgens [6].

### Polycystic ovary syndrome (PCOS)

Individuals afflicted with this prevalent illness may experience menstrual cycles that are not regular. In addition, they may have ovarian enlargement characterized by the presence of small fluid-filled structures known as follicles within each ovary. These follicles are visible during an ultrasound examination. Individuals with Polycystic Ovary Syndrome (PCOS) typically exhibit a higher number of follicles in their ovaries compared to individuals without the condition. Individuals afflicted with this prevalent illness may experience menstrual cycles that are not regular. In addition, they may have ovarian enlargement characterized by the presence of small fluid-filled structures known as follicles within each ovary. These follicles are visible during an ultrasound examination. Individuals with Polycystic Ovary Syndrome (PCOS) typically exhibit a higher number of follicles in their ovaries compared to individuals without the condition.. There are various genes like CYP 17 [Enzyme cytochrome P450-C17], CYP 19[Cytochrome P450 aromatase] are associated with the androgen synthesis pathway and INSR [Insulin receptor], CAPN10 [Calpain 10 protein] and IRS1, IRS2 [Insulin receptor substrates IRS1 and IRS2] are associated with insulin secretion and action implicated in PCOS aetiology.Mutations in the FMR1 gene can cause Fragile X-associated primary ovarian insufficiency (FXPOI), leading to irregular menstrual cycles and early menopause [7].

### Premature ovarian failure [POF/POI]

The lack of normal ovarian function before the age of 40 is referred to as premature ovarian failure. Primary ovarian insufficiency is another name for this illness, which causes irregular or sporadic periods that might last for years.[8]Altered methylation of genetic material, which triggers the suppression of genes, decreases the expression of genes, alters the chromatin structure and inevitably regulates key stages of development like inactivation of the X chromosome and genome-wide imprinting, is one of the main epigenetic markers of the epigenetic reprogramming that occurs during the ageing of germ cells. The absence of oocytes in the primordial follicle pool is associated with primary [POI], and epigenetic modification is important in controlling programmed oocyte death when the primordial follicle pool (PF) is forming [9].

### Pelvic inflammatory disease (PID)

Pelvic inflammatory disease (PID) is an inflammatory condition affecting the upper genital tract in women, caused by an infection. Usually, it is an infection that moves upwards, starting from the lower genital tract. The recommended treatment involves using antibiotics that target the main disease-causing microorganisms. Various medications can regulate the IL-17 signalling pathway, which in turn can attract neutrophils to the site of inflammation. This recruitment leads to the release of

myeloperoxidase (MPO) and the activation of gene expression for LCN2 and matrix metalloproteinases (MMPs). These processes ultimately boost the immune function of the body and ameliorate symptoms of pelvic inflammatory disease (PID). The regulation of anti-inflammatory and immunological systems in PID involves the modulation of T cells, B cells, IG, cytokines (such as IL-6, TNF-α, and IL-1β), prostaglandin-endoperoxide synthase 2 (PTGS2), matrix metalloprotein-9 (MMP9), and TLRs signalling pathways [10].

### Uterine fibroids

Uterine fibroids are non-cancerous growths that develop in the uterus. They have the potential to induce excessive and protracted menstrual bleeding. Following the use of tampons, you experience an abrupt rise in body temperature and a sensation of illness. Several variables, such as growth factors and WNT/β-catenin signalling, have been demonstrated to have a role in the development of uterine fibroids [11].

### Cervical Stenosis

The narrowness of the cervix restricts the passage of blood, resulting in increased pressure and pain in the uterus. Adenomyosis is a medical disorder characterized by the invasion of the endometrium (the inner lining of the uterus) into the muscular wall of the uterus. Adenomyosis can lead to dysmenorrhea, lower abdominal discomfort, and abdominal distension before menstruation, and can lead to menorrhagia. Endometriosis is a highly distressing medical disorder characterized by the abnormal implantation of uterine tissues in many locations throughout the body, particularly the fallopian tubes, pelvic tissues, and ovaries. This illness also leads to menstruation irregularities and discomfort [12].

## Factors Affecting Menstrual Cycle

### Body's stress response

The body's stress response, principally controlled by the hypothalamic-pituitary-adrenal (HPA)axis, has a substantial impact on menstrual function.One way in which stress affects menstruation function is through the dysregulation of the body's stress reactions, particularly within the hypothalamic-pituitary-adrenal axis. The hypothalamus controls the menstrual cycle by releasing the gonadotropin-releasing hormone, which stimulates the periodic release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. FSH plays a crucial role in the development of follicles, while LH controls the release of estradiol by the maturing follicle, which is necessary for ovulation. After ovulation, LH also aids in the maintenance of the corpus luteum [13].

### Intake of junk food

Junk food is generally deficient in vital nutrients such as vitamins, minerals, and fibre. Foods high in saturated fatty acids can disrupt the metabolism of progesterone during the luteal phase of the menstrual cycle, resulting in premenstrual symptoms. Due to their lack of micronutrients such as vitamin B6, calcium, magnesium, and potassium, junk foods can lead to hormonal imbalances and contribute to premenstrual syndrome (PMS) and other menstrual abnormalities [14].

### Obesity

There are multiple well-established mechanisms that link adipose tissue to ovulation and the menstrual cycle: Adipose tissue, or fat tissue, undergoes aromatization to convert androgens into estrogen. This transformation occurs place in different regions of the body, including the breast, belly, omentum, and adipose tissue within long bones [15]. Body weight has an impact on the direction of estrogen metabolism. Underweight women create a less powerful type of estrogen (2-hydroxylated form), whereas overweight women produce more strong forms of estrogen as a result of increased estrogenic activity (16-hydroxylated form). Obese women exhibit a reduced ability for estrogen binding with the SHBG protein, resulting in the deactivation of estrogen and an elevation in the proportion of unbound serum estradiol. In obese women, adipose tissue retains steroid hormones and can potentially regulate ovarian function by affecting the hypothalamic-pituitary axis [16].

### Skipping breakfast

Breakfast habits correlate with physiological, psychological, and social well-being. Omitting breakfast has a more pronounced impact on both waist circumference and BMI. There is a clear correlation observed worldwide between skipping breakfast and becoming overweight or obese.[17]In adults, the act of intentionally not eating meals may be associated with an elevation in body weight, a decrease in the body's ability to respond to insulin, and an increase in the concentration of lipids during periods of fasting. The consumption of breakfast directly impacts blood glucose levels, which in turn directly affects cognitive function [13].

### Lack of physical activity

Engaging in regular physical activity daily has several benefits for the body. It helps to maintain a healthy body weight, increases insulin sensitivity, boosts the basal metabolic rate (BMR), and stimulates the release of endorphins. These endorphins, in turn, contribute to the regulation of the menstrual cycle, improvement in conditions such as polycystic ovary syndrome (PCOD) and hypothyroidism, decrease in premenstrual syndrome (PMS), and an overall sense of well-being [18]. The most significant correlation with irregular periods is observed in those with low levels of physical activity. Obese and sedentary women have a greater occurrence of irregular periods compared to physically active women with normal weight. Excessive accumulation of fatty tissue can impact the levels of androgens and estrogens through multiple

mechanisms. It can serve as a storage site for fat-soluble steroids and influence the interactions between hormones and sex-hormone–binding globulin [19].

### Menstrual Disorders and Genetic Alterations

### PCOS(polycystic ovarian syndrome)

PCOS is categorized as an intrinsic condition of the ovaries, distinguished by an excessive production of androgen due to particular genetic defects. Luteinizing hormone stimulates the production of androgen in the ovarian theca cells. The rate-determining step in the production of steroidal hormones is the function of 17α hydroxylase and 17, 20 lyase enzymes in the theca cells. The cells exhibit the expression of the CYP17A1 gene, which codes for the P450c17 enzyme that is accountable for the previously mentioned procedure. The given text represents a list containing the numbers 49 and 50. The creation of androgens involves both activities that occur within the ovaries and processes that occur outside of the ovaries. Increased concentrations of the luteinizing hormone cause a decline in LH receptors, leading to a subsequent decrease in CYP17A1 expression and limiting the production of androgens. Insulin and insulin-like growth factors (IGFs) increase the overexpression of LH receptors and P450c17. The user's text is "[51]". In many in-vitro studies, it has been found that PCOS theca cells exhibit increased androgen production compared to normal control cells. The excessive synthesis of androgens is caused by hyperactive 17α hydroxylase and 17, 20 lyase enzymes. The number 52 is enclosed in square brackets.
Typically, around 20-30% of women diagnosed with polycystic ovarian syndrome (PCOS) experience increased levels of androgens in both their ovaries and adrenal glands, specifically dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) [20].

Various genes have been discovered to be linked with hyperandrogenism in PCOS during the evaluation and identification procedures. The CYP19 gene is responsible for the enzymatic activities of aromatase p450, which are necessary for the synthesis of estrogen. This gene is situated on the 15q21.2 chromosome. PCOS individuals who are lean or obese exhibit reduced aromatase activity [21]. The enzyme P450c17α, synthesized by the CYP17 gene, catalyzes the conversion of pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. A correlation was found between the excessive expression of CYP17 in theca cells and a genetic variation in the promoter region, which is associated with PCOS.[87–89].The CYP21 gene is responsible for generating an enzyme that converts 17-hydroxyprogesterone to 11-deoxycortisol, which is a crucial step in the manufacture of steroid hormones. The enzyme's lack of activity results in inefficient synthesis of steroids, which in turn contributes to the development of PCOS[22].The enzyme responsible for the critical step that controls the rate of conversion of cholesterol to progesterone is encoded by the CYP11a gene [23]. Various scientific investigations have discovered a connection between CYP11a and PCOS since there have been reports of polymorphism and variation in CYP11a. 92 Molecular studies have shown that at the post-transcriptional level, there are changes in CYP17A1 mRNA in theca cells from individuals with PCOS compared to normal cells. Specifically, the half-life of CYP17A1 mRNA is twice as long in theca cells from PCOS, resulting in higher levels of CYP17A1 mRNA and increased production of the CYP17A1 enzyme. This increased enzyme production promotes the synthesis and secretion of androgens in PCOS [20].

### Amenorrhea

Typically, cases of primary amenorrhea exhibit aneuploidy in the karyotype, specifically affecting the X chromosome. These anomalies lead to the emergence of several different conditions in patients, such as Turner syndrome (45, X) and numerous kinds of mosaic Turner syndrome with varying karyotypes.Loss of the second X chromosome leads to underdeveloped ovaries (streak ovaries), which cannot produce sufficient hormones for menstrual cycles, causing primary amenorrhea.Absence of menstruation (primary amenorrhea) caused due toMutations in the androgen receptor (AR) gene on the X chromosome. Individuals with a 46, XY karyotype have a functional inability to respond to androgens, leading to the development of female external genitalia and absence of menstruation[18].Functional hypothalamic amenorrhea (FHA) is a condition characterized by the transient and non-organic disruption of the regular release of gonadotropin-releasing hormone (GnRH). The three primary types of FHA are stress-induced amenorrhea, amenorrhea caused by weight reduction, and amenorrhea resulting from excessive exercise. The range of GnRH-luteinizing hormone (LH) disruptions in functional hypothalamic amenorrhea (FHA) is extensive and encompasses a lower average frequency of LH pulses, a total lack of LH pulsatility, a secretion pattern that seems normal, and a greater average frequency of LH pulses. Several neuropeptides, neurotransmitters, and neurosteroids have significant functions in the physiological control of GnRH pulsatile production. There is evidence suggesting that various neuropeptides may be implicated in the pathophysiology of functional hypothalamic amenorrhea (FHA) [24].
FHA is primarily linked to psychological distress. Severe stressors, such as strict diets, intense psychological stress, or severe exercise, might disturb the action of the hypothalamic-pituitary system that regulates ovarian function [25].

### Menoreghia

Menorrhagia, also known as heavy menstrual bleeding, is a condition characterized by excessively heavy or prolonged menstrual periods. Idiopathic Ovulatory Menorrhagia type of menorrhagia is characterized by regular, heavy menstrual bleeding that occurs without any identifiable pelvic pathology (such as fibroids or polyps) or general

bleeding disorder. Imbalances or abnormalities in prostaglandins (hormone-like substances involved in pain and inflammation) may be linked to idiopathic menorrhagia and heavy bleeding associated with fibroids, adenomyosis and external factors and intrauterine devices.Genetic mutations affecting blood clotting can lead to menorrhagia.Von Willebrand Disease (VWD): A hereditary bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor, a key protein in blood clotting [6].

**Dysmenorrhea (Painful Cramps)**

Dysmenorrhea refers to the occurrence of intense and frequent cramping during the menstrual period. Discomfort arises in the lower abdominal region but may extend to the lower back and thighs. Dysmenorrhea is commonly categorized as primary or secondary. Primary dysmenorrhea refers to the occurrence of cramping pain as a result of menstruation. The cramps arise due to uterine contractions and are typically more intense after episodes of heavy bleeding. Secondary dysmenorrhea refers to the discomfort experienced during menstruation that is associated with an underlying medical or physical problem, such as endometriosis or uterine fibroids. The number 20 is enclosed in parentheses.ESR1 and ESR2 genes encode estrogen receptors. Estrogen can increase the sensitivity of the uterus to prostaglandins. Genetic variations in estrogen receptor genes may affect estrogen levels and receptor sensitivity, influencing dysmenorrhea severity [6].

Dysmenorrhea is a condition characterized by inflammation in the body. It is crucial to steer clear of foods that can exacerbate the inflammatory reaction. Consuming high glycemic meals is associated with elevated amounts of inflammatory substances in the body, such as PGF2. Hence, it is crucial to consume food that has anti-inflammatory properties or adhere to an anti-inflammatory diet [26].

**Postpartum haemorrhage and sepsis**

Uterine fibroids are non-cancerous growths that develop in the uterus. They can induce excessive and protracted menstrual bleeding. Following the use of tampons, you experience an abrupt onset of elevated body temperature and a general feeling of illness. Several variables, such as growth factors and WNT/β-catenin signalling, have been demonstrated to have a role in the development of uterine fibroids[11]. Leiomyoma is the predominant kind of solid tumour found in women of reproductive age, occurring in approximately 20-25% of cases. While fibroids may not show any symptoms, they frequently lead to many health issues in women, such as menorrhagia (excessive menstrual bleeding), persistent pelvic pain, pressure on other pelvic organs, repeated miscarriages, complications during childbirth, postpartum bleeding, and infection [27].

Increasing data indicates that other variables, including growth factors and peptides, play a role in controlling the formation of leiomyomas. The growth of fibroids is defined by a mix of variables, including an increased deposition of extracellular matrix, changes in blood vessel distribution, and cell proliferation [28].

When sex hormones are present, smooth muscle cells (SMCs) in leiomyomas exhibit comparable ultrastructural characteristics to those of well-differentiated myometrial cells. The cells have a spindle shape, with ellipsoid nuclei and a length of 50-100 mm. However, they may have a reduced number of cytoplasmic filaments. The mitotic activity of smooth muscle cells (SMCs) in leiomyomas increases with the start of the secretory phase and remains high until menstruation [11]. Oxidative stress has been demonstrated to be a significant contributor in prevalent gynecologic illnesses, including fibroids, endometriosis, and surgical adhesions. Fibroids are non-cancerous tumours that originate from the smooth muscle cells in the wall of the uterus. They consist of a significant quantity of extracellular matrix, including collagen, proteoglycan, and fibronectin. Fibroids are enclosed by a thin layer of connective tissue and compressed muscle fibres.

Transforming growth factor Beta plays a pivotal function in the growth of fibroids. TGF-beta promotes the synthesis and accumulation of extracellular matrix (ECM) and is recognized as a key growth factor in the progression of fibrotic illness. TGF-beta, which is excessively produced in fibroids, exerts regulatory control and contributes to the development of fibrosis. Gonadotropin-releasing hormone (GnRH) agonists can suppress the production of TGF-beta. GnRH agonists alter osmotic pressures and reduce the water content of fibroids [29].

**Premenstrual syndrome**

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are caused by hormonal changes that occur after ovulation. The symptoms can manifest during the early, middle, or late luteal phase and are not linked to precise levels of any particular gonadal or non-gonadal hormone. While there is no conclusive evidence of a hormonal anomaly, the symptoms of premenstrual illnesses are linked to the ovary's synthesis of progesterone. The GABArgic and serotonergic systems are the two most well-studied and significant neurotransmitter systems involved in the development of the symptoms. The corpus luteum of the ovary and the brain produce metabolites of progesterone that bind to a specific site on the membrane of the gamma-aminobutyric acid (GABA) receptor [30]. This binding alters the receptor's structure, making it unresponsive to further activation and ultimately reducing the inhibitory effects of central GABA. The user's text is empty. A 'variant' PMD refers to a condition where the symptoms may be caused by the worsening of an underlying physical or mental disease, the use of external progestogens, or ovarian activity without ovulation [31].

**POI (Premature ovarian insufficiency)**

Premature ovarian insufficiency (POI) is a medical condition that is defined by the absence of menstruation for a minimum of 4 months, low levels of estrogen in the

body, and high levels of gonadotropins in the blood. Specifically, it is diagnosed when two separate blood tests taken at least one month apart show follicle-stimulating hormone (FSH) concentrations of over 40 IU/L in women under the age of 40, which is more than two standard deviations below the average age of menopause [32].

Premature ovarian insufficiency can result from an early exhaustion of the primordial follicle reservoir. Acquired ovarian insufficiency can also arise due to various conditions that lead to the destruction or loss of ovarian tissue, such as endometriosis, ovarian surgery, chemotherapy, or radiotherapy. It can also occur as a result of ovarian follicle dysfunction, ovarian follicle depletion, or mutations in genes linked to primary ovarian insufficiency. Chromosome abnormalities have long been acknowledged as a primary genetic factor. Premature ovarian insufficiency is primarily a consequence of ovarian follicle depletion in women who have numerical and structural abnormalities of the X chromosome. This depletion can be caused by an insufficient initial follicle number or by spontaneous rapid follicle loss [6].

Menstrual cycle complications and premature ovarian insufficiency (POI) that result from genetic factors can be regarded as either chromosomal mutations or induced by specific genes, which might impact either the X chromosome or autosomes. Both of these forms of disorders can be passed down through genetic inheritance. Thirteen percent of the cases are attributed to defects in the X chromosome, whereas six percent of the cases are caused by the premutation of the FMR1 gene [33].

Bone morphogenetic protein 15 (BMP15) and fragile X mental retardation 1 (FMR1), which are both situated on the X chromosome, are clearly significant determinants in the development of premature ovarian insufficiency. Nevertheless, there have been suggestions that other genes on the X chromosome may contribute to ovarian failure, namely in females with 45, X. However, this hypothesis has not been proven. The BMP15 gene can be located in one of the "POF critical regions" known as locus POF4 (MIM number 300510). It is located on the proximal region of the X chromosome, specifically on the Xp11.2 locus [12].

The duplication of BMP15 resulted in the preservation of a specific number of functional follicles at the age of pubertal development and the capacity to compensate, at least partially, for the loss of one copy of the other X-linked genes. The theory that BMP15 is the first ovary-determining gene to have been found on the X chromosome is supported by the fact that the BMP15 gene contributes to the ovarian phenotype of 45,X patients. This provides more evidence for the idea that inactivating mutations in this gene can predispose to points of interest (POI) [7].

The fact that chromosomal abnormalities are the underlying cause of menstrual cycle disorders, recurrent miscarriages, and early ovarian insufficiency has been known for a very long time. Depletion of ovarian follicles is the most common cause of premature ovarian insufficiency in women who have X chromosomal abnormalities. This depletion can be the result of either a low initial follicle amount or spontaneously accelerated follicle loss. The degree of X chromosomal mosaicism and the ramifications it has for reproduction are topics that are currently being discussed but not yet resolved [34].

**Table 1.1 The Hormonal Changes and Results of Menstrual Disturbances That Were Observed in Various Endocrine Disorders [18]**

| Type of disorder | Type of Menstrual Disturbance | Possible Mechanism |
|---|---|---|
| **Diabetes** | Oligomenorrhea, long cycles, long and heavy menstruation | Increased LH/FSH ratio and androgens, decreased gonadotrophin levels, hyperinsulinemia. |
| **PCOS** | Long and irregular menstrual cycles, secondary amenorrhea,oligomenorrhea | Increased LH and androgen secretion, prolonged exposure to estrogen. |
| **Hypothyroidism** | Irregular menses, heavy bleeding, oligomenorrhea, amenorrhea, breakthrough bleeding | Deceased SHBG, estradiol (E2), testosterone levels |
| **Cushing's syndrome** | Amenorrhea, oligomenorrhea, polymenorrhea | Ovarian damage, androgens, hypercortisolism |
| **Hyperprolactinemia** | Amenorrhea, oligomenorrhea, bleeding between cycles, polymenorrhea, hypermenorrhea and menometrorrhagia. | Inhibition of LH GnRH and maybe FSH |

**Treatment of Menstrual Disorders**

Changing your lifestyle is the greatest method to control menstruation issues (of course, after consulting with experts: preferably, your endocrinologist, nutritionist, and gynaecologist). Exercise and a well-balanced diet which are low in sugar and carbohydrates and high in protein and fibre are the best approaches for managing PCOS, PID,

and other associated ailments. Additionally, this slows down part of the weight gain, which is helpful because even a 5% weight drop makes therapy much simpler. Depending on the situation, a person may receive medication to help balance their hormones. Second-line therapies include ovarian drilling, laparoscopic surgery, and aromatase inhibitors might even be required in some cases. For particular treatment of certain symptoms, people may also visit different medical professionals [35].

### Nutritional Considerations

Proper nutrition is crucial, especially while dealing with Dysmenorrhea, which is an inflammatory condition. Therefore, it is essential to steer clear of foods that promote an inflammatory reaction. Consuming high glycemic meals is associated with elevated amounts of inflammatory substances in the body, such as PGF2. Hence, it is crucial to consume food that has anti-inflammatory properties or adhere to an anti-inflammatory diet [30].

Vitamin D is essential for the metabolism of calcium and the maintenance of bone health. Vitamin D is a secosteroid hormone that has progesterone-like action [25]. Vitamin D supplementation can improve insulin sensitivity and hormonal balance in women with Polycystic Ovary Disorder (PCOD), especially when taken daily by individuals with a deficiency [74]. Vitamin D is believed to affect the development of PCOD by regulating gene transcription, and hormonal modulation affects insulin metabolism and the regulation of fertility [4, 5].

Calcium and Vitamin D have a cooperative effect in diminishing the intensity of PMS symptoms. They control the balance of calcium in the body and affect the secretion of parathyroid hormone, which can have an effect on muscular function and mood. High-fiber diets aid in the regulation of estrogen levels by facilitating the elimination of estrogen through the digestive tract. This can mitigate the likelihood of estrogen-dominant diseases such as excessive menstrual bleeding and premenstrual syndrome (PMS) [16].

Vitamin E functions as an antioxidant, effectively counteracting the harmful effects of free radicals. When used in conjunction with other nutrients such as coenzyme Q10 or omega-3 fatty acids, it has demonstrated potential in enhancing insulin resistance and decreasing testosterone levels in women with PCOD [6]. Vitamin C should be studied as a possible treatment to enhance the structure of the ovaries and address the lack of ovulation associated with polycystic ovary syndrome (PCOS). The absorption of ascorbic acid during the period before ovulation is likely to support the occurrence of healthy ovulation. Ascorbic acid enhances the production of progesterone and oxytocin, and it is found in high levels in the corpus luteum [36].

Magnesium supplements alleviate PMS symptoms including physical discomfort, melancholy, irritability, emotional instability, and fluid accumulation. Magnesium aids in the relaxation of smooth muscle tissue. Research has demonstrated a significant reduction in menstrual cramps [12, 37].

Folic acid, also known as Vitamin B-9, is a man-made version of folate and plays a crucial role in a range of metabolic processes, including the production of DNA and RNA. Vitamin B6 plays a role in the production of neurotransmitters including serotonin and dopamine, which have an impact on mood and can alleviate symptoms of premenstrual syndrome (PMS). Additionally, it aids in the metabolism of estrogen, which may potentially alleviate symptoms associated with menstruation disorders [38].

### Eliminate sugary foods and processed sugar

Select minimal quantities of honey or agave. Opt for Stevia as a sweetener whenever feasible. Dairy products can cause congestion in the body, and several doctors have observed a decrease in menstrual cramp pain among women who stopped consuming dairy products. If you opt for dairy products, it is advisable to exclusively buy organic or organic raw dairy to prevent the presence of additional hormones. Excessive consumption of sugar might result in the development of insulin resistance. Elevated insulin levels have the potential to disturb the equilibrium of hormones. More precisely, it can cause the ovaries to produce higher levels of androgens. Polycystic ovarian syndrome (PCOS), a prevalent menstruation condition, is characterized by elevated androgens.[27]

### Reduce red meat and egg yolk consumption

The reason for this is that both red meat and egg yolk contain significant amounts of arachidonic acid (AA). It has been discovered that this leads to an increase in cellular inflammation. Reducing the consumption of red meat can lead to a drop in levels of inflammatory indicators, such as C-reactive protein (CRP) and interleukin-6 (IL-6). Limiting the consumption of these foods can aid in achieving a balanced omega-6 to omega-3 ratio, leading to a reduction in inflammatory reactions and an enhancement in overall hormonal well-being [3].

### Herbal Support

German Chamomile possesses analgesic properties, facilitates nerve relaxation, and mitigates anger, irritation, and depression, all of which are prevalent symptoms experienced during menstruation. Lavender oil, derived through distillation from the flower spikes of specific lavender species such as Lavandula latifolia from the Lamiaceae family, has the ability to alleviate symptoms of anxiety, despair, and menstrual discomfort. Clary Sage oil, derived from the buds and leaves of the Salvia Sclarea plant through steam distillation, possesses the ability to regulate menstrual cycles and treat symptoms associated with menopause [6].

### Hormonal treatment

The combination of levonorgestrel (90 mg) and ethinyl estradiol (20 mg) resulted in some improvements in premenstrual syndrome, however, the effects were not always constant. The treatment options for preventing PMS and PMDD include the combined oral contraceptive pill and GnRH analogues. A GnRH analogue is a man-made peptide that binds to a GnRH receptor and triggers the release of follicle-stimulating hormone and luteinizing hormone from the anterior pituitary gland. Following the initial increase in ovarian steroid production, it subsequently inhibits ovarian steroid production, leading to a state of 'medical menopause' and the consequent alleviation of PMS symptoms. Studies have demonstrated that using a high dosage of transdermal estradiol (200 mg) using a patch might effectively inhibit ovulation and alleviate symptoms associated with premenstrual syndrome (PMS).[39] Unopposed estrogen can result in the development of endometrial hyperplasia and cancer. However, research has indicated that taking oral progesterone may exacerbate symptoms of premenstrual syndrome (PMS) [40].

### Antiandrogen treatment

Antiandrogen medication is essential in the therapeutic management of hirsutism and acne. Contraception is necessary while administering antiandrogens to women of reproductive age due to the potential danger of feminization of the male fetus. The number is 18. The impact of the androgen receptor antagonist flutamide on the metabolic characteristics of polycystic ovary syndrome (PCOS). Studies conducted on both lean and obese patients with polycystic ovary syndrome (PCOS) have demonstrated that flutamide therapy had either a neutral or slightly positive impact on insulin sensitivity [41].

### Clomiphene

It functions by inducing the secretion of necessary hormones for ovulation. It inhibits the transmission of negative feedback signals, resulting in elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones play a vital role in the development and release of eggs from the ovaries. Clomiphene enhances the likelihood of pregnancy for women experiencing difficulties in conceiving by stimulating ovulation [28].

### Spironolactone

Spironolactone functions by inhibiting the actions of a hormone known as aldosterone within the body. It is classified as a potassium-sparing diuretic, meaning it aids in eliminating excess fluid from the body while preserving potassium. Spironolactone possesses anti-androgenic characteristics alongside its diuretic effects. It has the ability to inhibit the activity of androgens, which are male hormones, within the body. This can be beneficial in cases such as PCOS, where there is an overabundance of androgens. Spironolactone helps alleviate symptoms associated with PCOS, such as acne, excessive hair growth, and hair loss, by lowering testosterone levels in women [42].

### Letrozole

Femara, commonly known as letrozole, functions by inhibiting the aromatase enzyme. This enzyme is accountable for the conversion of androgens (male hormones) into estrogens (female hormones). Letrozole decreases estrogen levels in the body by blocking the action of aromatase. This can help slow down or stop the growth of estrogen-sensitive breast cancer cells [21].

## Conclusion

Menstrual problems are complex in terms of their pathogenesis. Timely identification and treatment of menstruation abnormalities can be beneficial for patients, as it can prevent or delay the need for long-term interventions. The diagnostic perspective on menstruation problems has significantly improved due to developments in genetics. The functional data obtained from several epigenetic and genome-wide association studies (GWAS) have significantly enhanced our understanding of the aetiology of menstruation disorders. These studies have also aided in identifying the underlying cause of these disorders in relation to chromosomal alterations. Genetic markers have enhanced the detection and treatment of reproductive and metabolic conditions, while also enabling differentiation between patients with specific disease characteristics. Early detection of menstruation diseases and their accompanying comorbidities is crucial for tailoring specialized treatments to each patient's unique phenotype. This necessitates ongoing advancements in genetic and pathophysiological research. A holistic approach to treating menstrual disorders involves combining dietary changes, lifestyle modifications, and appropriate medical interventions. Reducing the intake of sugary foods, processed sugars, red meat, and egg yolks can significantly impact hormonal balance, inflammation, and overall health. Regular exercise, stress management, and maintaining a healthy weight further support menstrual health. Medical treatments, including medications and potentially surgery, play a crucial role in managing more severe cases. Regular monitoring and a personalized approach ensure the best outcomes for individuals suffering from menstrual disorders.

## Funding

There is no funding involve

## Acknowledgement

Not Declared

## Conflict of Interest

The authors have no conflict of interest

## Inform Consent

No need of any informed consent in this paper

## Ethical Statement

This review is following all the relevant ethical aspects

## Author Contribution

All the authors have the equal contribution

## References


1. Rondanelli M, Perna S, Faliva M, Monteferrario F, Repaci E, Allieri FJAog, et al., "Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena," vol. 290pp. 1079-92, 2014.
2. Zehravi M, Maqbool M, Ara IJIjoam, health, "Polycystic ovary syndrome and infertility: an update," vol. 34(2), pp. 1-9, 2022.
3. Jeanes Y, Barr S, Smith K, Hart KJJohn, dietetics, "Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians," vol. 22(6), pp. 551-8, 2009.
4. Küçükaydoğan N, Şavk E, Uslu M, Şendur N, Karaman G, Demirkan SJTTADV, "Relationship of cutaneous moisture, sebum and pH changes of healthy skin with menstrual cycle," vol. 54(3), pp. 90-5, 2020.
5. Akhila G, Shaik A, Kumar RDJIJRHCP, "Current factors affecting the menstrual cycle," vol. 2(1), pp. 18-21, 2020.
6. Schweiger U, Tuschl RJ, Platte P, Broocks A, Laessle RG, Pirke K-MJF, et al., "Everyday eating behavior and menstrual function in young women," vol. 57(4), pp. 771-5, 1992.
7. Faghfoori Z, Fazelian S, Shadnoush M, Goodarzi RJD, research msC, reviews, "Nutritional management in women with polycystic ovary syndrome: A review study," vol. 11pp. S429-S32, 2017.
8. Khalil NM, Carraro E, Cótica LF, Mainardes RMJEoodd, "Potential of polymeric nanoparticles in AIDS treatment and prevention," vol. 8(1), pp. 95-112, 2011.
9. Wang J, Sun X, Yang Z, Li S, Wang Y, Ren R, et al., "Epigenetic regulation in premature ovarian failure: A literature review," vol. 13pp. 998424, 2023.
10. Si L, Yin M, Wang J, Yang S, Zhang J, Wei LJERoP, et al., "Evaluation of quality of pharmacoeconomic studies involved in traditional Chinese medicine in China," vol. 21(5), pp. 1049-60, 2021.
11. Kimura F, Tsuji S, Murakami T. Molecular Pathogenesis of Uterine Fibroids. In: Sugino N, editor. Uterine Fibroids and Adenomyosis. Singapore: Springer Singapore; 2018. p. 37-57.
12. Manore MMJSm, "Dietary recommendations and athletic menstrual dysfunction," vol. 32pp. 887-901, 2002.
13. Segars JH. Fibroids: John Wiley & Sons; 2012.
14. Barnett RJTL, "Cushing's syndrome," vol. 388(10045), pp. 649, 2016.
15. ÇAYKÖYLÜ A, Capoglu I, ÖZTÜRK IJP, neurosciences c, "The possible factors affecting suicide attempts in the different phases of the menstrual cycle," vol. 58(5), pp. 460-4, 2004.
16. Kovanci E, Schutt AKJO, America gcoN, "Premature ovarian failure: clinical presentation and treatment," vol. 42(1), pp. 153-61, 2015.
17. Bahamondes L, Ali MJFr, "Recent advances in managing and understanding menstrual disorders," vol. 7pp., 2015.
18. Ajith DMJJoPSP, "Nutritional management of PCOS: A review article," vol. 6(8), pp. 8979-84, 2022.
19. VanKoevering KK, Sabetsarvestani K, Sullivan SE, Barkan A, Mierzwa M, McKean ELJJoNSPBSB, "Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening," vol. 81(01), pp. 075-81, 2020.
20. Penzias A, Bendikson K, Butts S, Coutifaris C, Falcone T, Fossum G, et al., "Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline," vol. 108(3), pp. 426-41, 2017.
21. Lusher JM, McMillan CW, Medicine HSGJTAJo, "Severe factor VIII and factor IX deficiency in females," vol. 65(4), pp. 637-48, 1978.
22. Murdock PJ, Woodhams BJ, Matthews KB, Pasi KJ, Goodall AHJT, haemostasis, "von Willebrand factor activity detected in a monoclonal antibody-based ELISA: an alternative to the ristocetin cofactor platelet agglutination assay for diagnostic use," vol. 78(10), pp. 1272-7, 1997.
23. Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TCJTJop, "Prevalence of von Willebrand disease in children: a multiethnic study," vol. 123(6), pp. 893-8, 1993.
24. Rapkin AJ, Akopians ALJMi, "Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder," vol. 18(2), pp. 52-9, 2012.
25. Obstetricians ACo, Gynecol GJO, "Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women," vol. 124(1), pp. 193-7, 2014.
26. Aguirre E, "Endocrine Disrupting Chemical Exposure in Feminine Hygiene Products and the Effect on the Menstrual Cycle," vol. pp., 2022.
27. Nowak RAJBP, Obstetrics RC, Gynaecology, "Fibroids: pathophysiology and current medical treatment," vol. 13(2), pp. 223-38, 1999.
28. Baum A, Nesselhof SE. Psychological research and the prevention, etiology, and treatment of AIDS: American Psychological Association; 1988.
29. Begum MS, Areen S, "Optimizing Polycystic Ovarian Disorder (PCOD) Treatment with Personalized Lifestyle and Nutrition Strategies," vol. pp., 2023.

30. Turkington RW, Lebovitz HEJTAJoM, "Extra-adrenal endocrine deficiencies in Addison's disease," vol. 43(4), pp. 499-507, 1967.
31. Hoek A, Schoemaker J, Drexhage HJEr, "Premature ovarian failure and ovarian autoimmunity," vol. 18(1), pp. 107-34, 1997.
32. March CMJRBO, "Management of Asherman's syndrome," vol. 23(1), pp. 63-76, 2011.
33. Sheehan H, Murdoch RJBAIJoO, Gynaecology, "Post-partum Necrosis of the Anterior Pituitary; Pathological and Clinical Aspects," vol. 45(3), pp. 456-87, 1938.
34. Steele S, Mason B, Brett AJBMJ, "Amenorrhoea after discontinuing combined oestrogen-progestogen oral contraceptives," vol. 4(5888), pp. 343-5, 1973.
35. Bakalov V, Vanderhoof V, Bondy C, Nelson LJHR, "Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure," vol. 17(8), pp. 2096-100, 2002.
36. Spencer JB, Badik JR, Ryan EL, Gleason TJ, Broadaway KA, Epstein MP, et al., "Modifiers of ovarian function in girls and women with classic galactosemia," vol. 98(7), pp. E1257-E65, 2013.
37. Bradlow J, Coulter A, Brooks P. Patterns of referral: a study of referrals to outpatient clinics from general practices in the Oxford region: Health Services Research Unit, Department of Public Health and Primary Care …; 1992.
38. Hallberg L, Hôgdahl A-M, Nilsson L, Rybo GJAoegS, "Menstrual blood loss–a population study: variation at different ages and attempts to define normality," vol. 45(3), pp. 320-51, 1966.
39. Hergenroeder AC, Smith EB, Shypailo R, Jones LA, Klish WJ, Ellis KJAjoo, et al., "Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months," vol. 176(5), pp. 1017-25, 1997.
40. Leppert P, Fouany M, Segars JHJf, "Understanding uterine fibroids," vol. pp. 1-10, 2013.
41. Daley AJBJoGP. The role of exercise in the treatment of menstrual disorders: the evidence. British Journal of General Practice; 2009. p. 241-2.
42. EVANS PCJO, Gynecology, "Obstetric and gynecologic patients with von Willebrand's disease," vol. 38(1), pp. 37-43, 1971.