MENSTRUAL DISORDERS

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Menstrual Disorders Clinical Guidance- Issued September 2020

Contents

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Abbreviations

ALLO	Allopregnanolone
AMH	Serum Anti-Müllerian Hormone
AUBL	Abnormal Uterine Bleeding associated with Leiomyomas
CBT	Cognitive Behavioral Therapy
CHI	Council of Health Insurance
COCPs	Combined Oral Contraceptive Pills
CPG	Clinical Practice Guideline
DHEAS	Dehydroepiandrosterone Sulfate
DRSP	Daily Record of the Severity of the Problem
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GAMSA	GABAa Modulating Steroid Antagonist
GnRH	Gonadotropin Releasing Hormone
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRT	Hormone Replacement Therapy
ICD-11	11th revision of the International Statistical Classification of Diseases
IDF	CHI Drug Formulary
ISPD	International Society for Premenstrual Disorders
ISPMD	International Society for Premenstrual Disorders
IVM	In Vitro Maturation
LNG-AUD	Levonorgestrel-Releasing Intrauterine Devices
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
PMDD	Premenstrual Dysphoric Disorder
PRISM	Prospective Record of the Impact and Severity of Menstrual Symptoms
PSST	Premenstrual Symptom Screening Tool
RCOs	Reactive Carbonyl Compounds
SFDA	Saudi Food and Drug Authority
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
UAE	Uterine Artery Embolization
WHO	World Health Organization

Executive Summary

Menstrual disorders are problems related to a woman's normal menstrual cycle[1]. Some common menstrual abnormalities include amenorrhea, abnormal uterine bleeding, dysmenorrhea, premenstrual syndrome (PMS), Premenstrual dysphoric disorder (PMDD) or polycystic ovarian syndrome (PCOS). Premenstrual symptoms are characterized by a variety of psycho-physical symptoms that are present in the luteal phase before menstruation and impair the quality of life of many women[2].

Premenstrual disorders are common in women of reproductive age and may be deemed physiological rather than pathological[3]. Epidemiological studies show that the prevalence of premenstrual symptoms, including mild cases, is very high, ranging from 80% to 90%[2]. Other studies showed that 24% of women aged 20–34 years had symptoms of moderate-to-severe PMS[4]. PMDD, is a severe form of PMS that interferes with women's daily life. Symptoms may include sharp mood swings, irritability, hopelessness, anxiety, problems concentration, changes in appetite, sleep problems, and bloating[5]. PMDD, at the most severe end of the spectrum, affects about 3–8% of women of reproductive age[6]. On another hand, Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting reproductive-aged women, with impacts across the lifespan from adolescence to post menopause[7]. Its prevalence is between 10% to 13% as confirmed in the guideline process[8,9].

Data on prevalence of menstrual disorders in Saudi Arabia Kingdom remains limited. One study examined the screening of premenstrual symptoms and self-medication acts among women in Riyadh, Saudi Arabia found that nearly half of persons who did not have PMS/PMDD self-medicated themselves thinking that they had PMS/PMDD[10]. Another study on prevalence of PCOS in the middle east and north Africa region (MENA) showed that in 2019, the age-standardized point prevalence of PCOS ranged from 1,213.1 to 2,838.1 (per 100,000 women) in the 21 countries and territories that comprise the MENA region and that Kuwait, Qatar and Saudi Arabia had the highest ones[11].

The type and severity of premenstrual disorders are influenced by age, race, ethnicity, and health status particularly mental health[12] . For some women, PMS symptoms can be so severe that they miss work or school, but milder symptoms may not bother others. PMDD, a similar but more serious health problem is attributed for causing serious irritability, depression, or anxiety in a week or two before a woman's period begins[10]. On the other hand, the etiology of PCOS is complex, and clinical presentation is heterogeneous with a combination of reproductive, metabolic, and psychological features[8,9].

Risk factors for PMS and PMDD include a timing aspect (dominated by neurotransmitters), a menstruation aspect (entailing physiological alterations coming before menses), and a vulnerability aspect (encompassing personality, susceptibility to depression, and attitude towards menstruation)[12]. Life stressors

and exogenous hormonal exposure were also found to have the most substantial impact on women diagnosed with PMS[13].

At the same time, economic burden of PMS and PMDD has been examined in literatures. The economic burden affiliated with PMDD was quantified in one report by assessing women's use of health care services, related expenditures, loss of work, limitation of roles, and reduced productivity. Women diagnosed with PMDD indicate reduced productivity levels within 5 to 10 days after the menses begin and the chances that a woman could use health care services increase as the severity of the symptoms increases[14].

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to menstrual disorders. The primary goal of the Council of Health Insurance in issuing menstrual disorders guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with menstrual disorders in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on Saudi, American, European and England guidelines issued within the last three years.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of bipolar disorder.

This report functions as an addendum to the prior CHI menstrual disorders report and seeks to offer guidance for the effective management of menstrual disorders.

Regarding the management of menstrual disorders, two new medications were approved by FDA for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, however, both are not registered by SFDA. No changes or modifications were made to existing drugs, but some drugs were withdrawn from Saudi FDA.

Below is a table summarizing the major changes based on the different menstrual disorders' guidelines used to issue this report:

Table 1. General Recommendations for the Management of Menstrual Disorders

Management of Menstrual Disorders		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Many symptoms of severe PMS/PMDD (irritability, anger, depression and labile mood) are the same as those experienced by	Not graded	Premenstrual disorders including premenstrual syndrome and premenstrual

women with other psychiatric disorders. Cyclicity of symptoms is key to the diagnosis.		dysphoric disorder, Royal College of Obstetricians and Gynecologists, 2023
The new DSM-5 criteria for PMDD require a combination of symptoms that began in the final week before menses, started to improve in the days after onset of menses and were absent in the postmenstrual weeks during the past year.	Not graded	Saudi Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)
At least one of 5 or more required symptoms must be marked lability of affect, irritability or anger or increased interpersonal conflict, depressed mood or hopelessness or self-deprecation, or marked anxiety or tension.	Not graded	Saudi Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)
PMS/PMDD is a chronic condition that, for now, can only be cured by removing the ovaries or by ovarian failure at the time of menopause. For most women, symptoms can be controlled during reproductive life. At the same time, treatments aim to achieve the greatest functional improvement possible.	Not graded	Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder, Royal College of Obstetricians and Gynecologists, 2023
Management options are either to reduce the effect of hormonal fluctuations linked with the menstrual cycle on neurotransmitter receptors (serotonin and GABAA). Or to inhibit the menstrual cycle by preventing ovulation	Not graded	Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder, Royal College of Obstetricians and Gynecologists, 2023
First line treatment includes reducing effect of hormone fluctuation on neurotransmitters through Lifestyle modification, Cognitive behavioral therapy (CBT)and Neuromodulators like Selective serotonin reuptake	Not graded	Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder, Royal College of

inhibitor [SSRI]/ Selective norepinephrine reuptake inhibitor [SNRI] Combined oral contraceptive pills also reduce fluctuations in hormone level.		Obstetricians and Gynecologists, 2023
When irregular menstrual cycles are present, a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines.	Strong recommendation	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	Strong recommendation, very low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Serum anti-Müllerian hormone (AMH) could be used for defining PCOM in adults.	Conditional recommendation, moderate quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Psychological therapy could be considered first-line management, and antidepressant medications are considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present.	Conditional recommendation	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome

Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioral strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	Strong recommendation, very low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Combined oral contraceptive pills (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	Conditional recommendation, very low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	Conditional recommendation, very low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Anti-obesity medications, including liraglutide, semaglutide, and both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	Conditional recommendation	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of 6 months of COCP and/or cosmetic therapy.	Conditional recommendation, very low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of

		Polycystic Ovary Syndrome
Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	Strong recommendation, high quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy, and live birth rates.	Conditional recommendation, low quality of evidence	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome

Section 3 lists the key recommendations synthesis for menstrual disorders treatment.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI menstrual disorder report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the 2020 CHI menstrual disorders report and the corresponding recommendations:

Ten guidelines were used in the last version of menstrual disorders. Updates were found for management of premenstrual Syndrome by the Royal College of Obstetricians and Gynecologists published in November 2018 and updated in 2023 and for the international evidence-based guideline for the assessment and management of polycystic ovary syndrome published in 2018 and updated in 2023.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
Heavy menstrual bleeding: assessment and management NICE guideline. Published: 14 March 2018 Last updated 31 March 2020	N/A*
American College of Obstetricians and Gynecologists: Screening and Management of Bleeding Disorders in Adolescents with Heavy Menstrual Bleeding 2019	N/A*
American College of Obstetricians and Gynecologists: Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women Committee Opinion Number 557 April 2013 Reaffirmed 2019	N/A*
SOGC Clinical Practice Guideline: Abnormal Uterine Bleeding in Pre-Menopausal Women, 2013 reaffirmed 2018	N/A*
American Academy of Family Physicians: Diagnosis and Initial Management of Dysmenorrhea 2014	N/A*
SOGC Clinical Practice Guideline: The Management of Uterine Leiomyomas 2015	N/A*
2016 American Academy of Family Physicians: Premenstrual Syndrome and Premenstrual Dysphoric Disorder.	N/A*
Royal College of Obstetricians and Gynecologists: Management of Premenstrual Syndrome, November 2018	Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder, Royal College of Obstetricians and Gynecologists, 2023
International evidence-based guideline for the assessment and management of polycystic ovary syndrome, 2018	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome.

2016 American Academy of Family Physicians: Diagnosis and Treatment of Polycystic Ovary Syndrome	N/A*

*: *No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 Premenstrual Disorders Including Premenstrual Syndrome and Premenstrual Dysphoric Disorder, Royal College of Obstetricians and Gynecologists (2023)

Premenstrual disorders include various psychological, behavioral, and physical disorders related to the hormones of the menstrual cycle.

The symptoms manifest during the luteal or post ovulation phase of the cycle and typically resolve by the end of menstruation.

The symptoms of premenstrual dysphoric disorder (PMDD) may be psychological, including depression, anxiety, mood swings, irritability and loss of confidence; or physical, including breast tenderness and abdominal bloating.

This guideline summarizes the etiology, diagnostic criteria, and up-to-date, evidence-based management options[3].

1. **Etiology**

It remains unknown why some women have a profound response to normal hormone levels produced during the menstrual cycle.

Possible theories include abnormal sensitivity of the central nervous system to female hormones, genetic factors or psychosocial factors, such as stress.

Crucial to the pathogenesis of PMS/PMDD is an increased sensitivity to hormonal fluctuations during a normal menstrual cycle, especially to progesterone and its GABAergic metabolite allopregnanolone, which is secreted following ovulation.

2. **Diagnosis**

In 2012, the International Society for Premenstrual Disorders (ISPMD) produced a classification of PMD, categorizing it into either ‘Core PMD’ or ‘Variants of PMD’. (Figure 1).

In 2013, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) of the American Psychiatric Association defined the diagnostic criteria for PMDD, at the most severe end of the spectrum, under Section II (depressive disorders), distinguishing it from mild to moderate PMS.

In May 2019, the World Health Organization (WHO) included PMDD in the 11th revision of the International Statistical Classification of Diseases, (ICD- 11). It was primarily listed in diseases of the genitourinary system, and cross listed in depressive disorders, highlighting the importance of multidisciplinary care for these women.

Essential diagnostic criteria for PMS/PMDD are:

- Relation of symptoms to the luteal phase of the ovarian cycle
- Relief of symptoms following the onset of menstruation
- Symptom-free period before ovulation
- Symptoms causing considerable distress and impairment to daily personal, professional or social commitments during the luteal phase.

3. Investigations

Many symptoms of severe PMS/PMDD (irritability, anger, depression and labile mood) are the same as those experienced by women with other psychiatric disorders.

Cyclicity of symptoms is key to the diagnosis.

Prospective recording of symptoms over two cycles using symptom diary charts is crucial, if possible, though may not be feasible in women at high risk of suicide.

Many PMS specific charts are available for symptom recording, including the 'Daily Record of the Severity of the Problem' (DRSP) and the 'Prospective Record of the Impact and Severity of Menstrual Symptoms' (PRISM) chart.

Table 3. Differences Between Mild/Moderate and Severe Premenstrual Syndrome (PMS), Including Premenstrual Dysphoric Disorder (PMDD). Adapted from National Association for Premenstrual Syndromes (NAPS)[15].

Parameter	Mild to moderate PMS	Severe PMS including PMDD
Prevalence (%)	50 – 80	3 – 8
Severity of symptoms	Mild to moderate	Severe
Presenting symptoms	Physical or emotional or both	Predominantly emotional
Diagnostic criteria	None	DSM-5 (PPMD)
Affective symptoms	May or may not be present	Always present
Who can manage	Usually managed in primary care	Mainly need a referral to secondary care/multidisciplinary care
Treatment	Can be managed with lifestyle modifications if mild	Mostly need pharmacological treatment May also need surgery

There are several important points to consider when a diagnosis PMS/PMDD is suspected:

- Prospectively complete the symptom diary over two cycles before starting treatment, if possible, to avoid recall bias.
- The cyclical pattern of symptoms distinguishes PMS/ PMDD from other psychiatric disorders.
- Other underlying medical and psychiatric disorders should be excluded and caution should be exercised during the assessment of women with a premenstrual exacerbation of an underlying psychiatric condition. The absence of a symptom-free interval makes a diagnosis of PMS/PMDD unlikely.
- When the diagnosis is in doubt, or comorbid conditions cloud the precise impact of the menstrual cycle on the overall clinical picture, a trial of medical ovarian suppression with a gonadotropin releasing hormone (GnRH) agonist can be helpful by temporarily eliminating ovarian hormone secretion.
- If symptoms occur after exogenous hormones, discontinue the hormones and review to exclude a medication-induced mood disorder.

There are no laboratory tests or investigations available to make a diagnosis of PMS/PMDD. Depending on the presentation, medical/psychiatric conditions should be excluded as an underlying cause by taking a full clinical history:

- Psychiatric: depression, dysthymia, anxiety, panic disorder, bipolar disorder, somatoform disorder, personality disorder, and substance abuse.
- Medical: anemia, autoimmune diseases, chronic fatigue syndrome, diabetes, seizure disorders, hypothyroidism, endometriosis, allergies, and ovarian cysts.

4. Treatment

PMS/PMDD is a chronic condition that, for now, can only be cured by removing the ovaries or by ovarian failure at the time of menopause.

For most women, symptoms can be controlled during reproductive life. At the same time, treatments aim to achieve the greatest functional improvement possible.

Based on the pathophysiology of PMS, the management options are either:

- to reduce the effect of hormonal fluctuations linked with the menstrual cycle on neurotransmitter receptors (serotonin and GABAA),
- or to inhibit the menstrual cycle by preventing ovulation.

Optimal management depends on a precise diagnosis, assessment of the severity and impact of symptoms, patient preference and response to the treatment.

It is imperative to listen to the patient carefully and empathetically, considering any previous treatment received and response to treatment, and tailoring the optimum treatment according to the patient's needs.

Different treatment options are available and some are delignated in the table below.

Table 4. Management of Premenstrual Syndrome (Adapted from Green et al 2016)

Evidence-based treatment approach	
First line: reduce effect of hormone fluctuation on neurotransmitters	**Lifestyle modification** - Complex carbohydrate diet during luteal phase - Aerobic exercise, yoga, meditation - Exposure to sunlight - Stop smoking/ alcohol Cognitive behavioral therapy (CBT) Neuromodulators (Selective serotonin reuptake inhibitor [SSRI]/ Selective norepinephrine reuptake inhibitor [SNRI] - Continuous, or - Luteal phase Combined oral contraceptive pills (reduce fluctuations in hormone level) For women not planning pregnancy: - Short hormone free interval 24/4 regimen of drospirenone 3mg and ethinyl estradiol 20 mcg. (Note: increased risk of venous thromboembolism (VTE) with drospirenone containing COCPs) - Combined oral contraceptive pills (COCPs) in continuous/ tricyclic pattern Levonorgestrel (LNG) 90 micrograms/ethinyl estradiol 20 micrograms continuously for 3 4 months without a break
Second line	- Combination therapy with SSRIs and COCPs - Estrogen therapy – estradiol patch (100 micrograms) or estradiol gel (3 milligrams) + micronized progesterone (200 milligrams for 12 days during luteal phase, orally or vaginally) or levonorgestrel intrauterine system (LNG IUS) 52 milligrams
Third line: reduce fluctuations in hormone level	GnRH analogues Add-back hormone replacement therapy (HRT) – GnRH agonists (monthly or 3-monthly injections) +/- add back HRT
Fourth line: reduce fluctuations in hormone levels	Total hysterectomy + bilateral salpingo-oophorectomy +/- HRT in refractory cases not responding to medical management.

Novel therapies (currently under research)	- 5-a reductase inhibitor (dutasteride) – dose 2.5 mg daily (reduce luteal phase increase in allopregnanolone). - Iso-allepregnanolone (UC1010) – sepranolone (GABAA modulating steroid antagonist inhibits allopregnanolone action) - Vitex agnus castus (VAC) – balances female sex hormones through its phytochemicals)

5. Neuromodulation

Neuromodulation can be achieved by increasing serotonin levels or blocking the effect of allopregnanolone.

Increased serotonin levels can be achieved by:

- Exercise: Exercise increases extracellular serotonin and its metabolite 5-HIAA in the hippocampus and cortex.
- Diet: A complex carbohydrate and tryptophan-rich diet, including foods like whole milk, canned tuna, cheese, and peanuts, can increase the amount of serotonin available centrally.
- Exposure to light: Human skin has an inherent serotonergic system capable
- of generating serotonin in response to light.
- Mood induction/stress reduction: the interaction between serotonin synthesis and mood is two-way, with serotonin influencing mood and mood influencing serotonin.
- Use of selective serotonin reuptake inhibitors (SSRIs)/ serotonin and norepinephrine reuptake inhibitors (SNRIs). These are increasingly used as first-line therapy.

Blocking the effect of allopregnanolone can be achieved by:

- Reducing progesterone metabolism by 5-a reductase inhibitor. Dutasteride (5-a reductase inhibitor) at a daily dose of 2.5mg, but not placebo, prevented the luteal phase increase in allopregnanolone and significantly reduced PMDD symptoms.
- Antagonizing the effect of allopregnanolone (iso-allopregnanolone). GABAa modulating steroid antagonist (GAMSA), sepranolone (UC1010), during the premenstrual phase in women with PMDD showed considerable improvement in PMDD symptom severity and impairment compared with placebo (comparable with SSRIs and drospirenone-containing oral contraceptives).
- Use of cognitive behavioral therapy (CBT).

6. Suppression of ovarian hormones

Combined oral contraception (COC): COC inhibits ovulation. Certain hormonal combinations in combined pills are suitable for women with no contraindications to combined hormonal contraception.

Short hormone-free interval (24/4), tricycling and continuous dosing are considered better than standard cyclical (21/7) treatment to control PMD with a reduction in hormonal fluctuations.

Estrogen-containing hormone replacement therapy (HRT) Inhibition of ovulation can be achieved using higher doses of estrogen (≥100 micrograms) delivered transdermally.

Endometrial protection is required and can be provided either by insertion of a levonorgestrel-containing intrauterine system, or by micronized progesterone (Utrogestan®) delivered for 12 days of each cycle in the dose of 200 milligrams per day.

A lower dose of 100 milligrams of Utrogestan and/or a shorter duration regime (7–10 days) may be used in progesterone-intolerant women.

Combining high-dose transdermal estrogen to override any underlying cyclical activity with micronized progesterone delivered either orally or per vaginum (out of product license) can be tried as second-line therapy if the standard first-line treatment fails.

If a suboptimal progesterone dose is used, women should have regular ultrasound monitoring of endometrial thickness.

Gonadotropin releasing hormone (GnRH) analogues: By inducing medical menopause, GnRH analogues provide relief from both physical and psychological symptoms of PMD.

GnRHa therapy is recommended in women with severe PMS/ PMDD.

The route of administration can be parental (for example, goserelin and leuprorelin) or intranasal (nafarelin).

If treatment is continued for more than 6 months, add-back hormone therapy and regular assessment of bone mineral density are recommended to reduce the long-term risks of estrogen deficiency.

Diagnosis of PMD should be questioned if symptom relief is not achieved after at least 12 weeks of GnRHa treatment.

Removal of both ovaries and the uterus with appropriate estrogen replacement is considered highly effective and is a well-accepted permanent cure for severe PMS/PMDD.

Surgery is beneficial if there are other indications for hysterectomy like fibroid uterus.

1.1.2 International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (2023)

The Clinical practice in the assessment and management of Polycystic Ovary Syndrome (PCOS) remains inconsistent, with ongoing key evidence-practice gaps.

Following on from the 2018 International Evidence-based Guideline for the Assessment and Management of PCOS independently evaluated as high quality, this extensive update integrates current literature with previous systematic reviews and extends to new clinical questions prioritized by consumers.

This guideline provides a single source of international evidence-based recommendations to guide clinical practice with the opportunity for adaptation in relevant health systems[7].

Material and Method

The guideline recommendations are presented by category, terms used, evidence quality and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework considerations (table 5).

Table 5. Categories of PCOS Guideline Recommendations

Category	Definition
EBR	Evidence Based Recommendations: Evidence sufficient to inform a recommendation made by the guideline development group
CR	Consensus Recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population
PP	Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

Evidence quality was categorized according to the GRADE framework, with judgments about the quality of the included studies and/or synthesized evidence incorporating risk of bias, inconsistency, indirectness, imprecision, and any other considerations that may influence evidence quality.

These judgments considered study number and design, statistical data and importance of outcomes and are described in table 6.

Table 6. Quality (Certainty) of Evidence Categories (Adapted from GRADE)

Category	Definition
High	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.

Low	Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

RECOMMENDATIONS FOR THE ASSESSMENT AND MANAGEMENT OF POLYCYSTIC OVARY SYNDROME (PCOS)

1. **Screening, diagnostic and risk assessment, and life stages**

    a. **Irregular cycles and ovulatory dysfunction**:

Irregular menstrual cycles are defined as follows:

- Normal in the first-year post menarche as part of the pubertal transition.
- 1 to <3 years post menarche: <21 or >45 days.
- 3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year.
- 1 year post menarche >90 days for any 1 cycle.
- Primary amenorrhea by age 15 or >3 years post thelarche (breast development).

When irregular menstrual cycles are present, a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines (CR, Strong recommendation).

The mean age of menarche may differ across populations (PP).

In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors (PP).

For adolescents who have features of PCOS, but do not meet diagnostic criteria, an “increased risk” could be considered, and reassessment is advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features, and those with significant weight gain in adolescence (PP).

Ovulatory dysfunction can still occur with regular cycles, and if anovulation needs to be confirmed, serum progesterone levels can be measured (PP).

    b. **Biochemical hyperandrogenism**

Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index (EBR, Strong recommendation, very low quality of evidence).

If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age-associated decrease in DHEAS (EBR, Conditional recommendation, very low quality of evidence).

Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation (EBR, Strong recommendation, low quality of evidence).

Laboratories should use LC-MS/MS assays over direct immunoassays (eg, radiometric and enzyme linked) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS (EBR, Strong recommendation, low quality of evidence).

For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (ie, hirsutism) (PP).

It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of 3 months and contraception should be managed otherwise during this time (PP).

Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role (PP).

In most adolescents, androgen levels reach adult ranges at 12-15 years of age (PP).

If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumor (PP).

Reference ranges for different methods and laboratories vary widely and are often based on an arbitrary percentile or variances of the mean from a population that has not been fully characterized and is highly likely to include women with PCOS. Normal values should be determined either by the range of values in a well-characterized healthy control population or by cluster analysis of general population values (PP).

Laboratories involved in androgen measurements in females should consider the following:

- Determining laboratory normal values either by the range of values in a well-characterized healthy control population or by cluster analysis of the values of a large general population.
- Applying the most accurate methods where available.
- Using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available.
- Future improvements may arise from measurement of 11-oxygenated androgens and from establishing cut-off levels or thresholds based on large-scale validation in populations of different ages and ethnicities (PP).

c. Clinical hyperandrogenism

The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults (EBR, Conditional recommendation, very low quality of evidence).

Healthcare professionals could recognize that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism EBR, Conditional recommendation, very low quality of evidence).

A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents (CR, Strong recommendation).

Healthcare professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity (CR, Conditional Recommendation).

A modified Ferriman-Gallwey score (mFG) of 4-6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment (CR, Strong recommendation)

Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity, but the prevalence of hirsutism appears similar across ethnicities (CR, Conditional Recommendation).

Healthcare professionals should (PP):

- Be aware that standardized visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas.
- Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss.

- Note that there are no universally accepted visual instruments for assessing the presence of acne.
- Recognize that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity.
- Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination.
- Note that only terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture, and are generally pigmented.
- Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumors and ovarian hyperthecosis.
- Monitor clinical signs of hyperandrogenism, including hirsutism, acne, and female pattern hair loss, for improvement or treatment adjustment during therapy.

d. Ultrasound and polycystic ovarian morphology

Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults (EBR, strong recommendation, low quality of evidence).

Follicle number per ovary (FNPO), follicle number per cross-section (FNPS), and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults (EBR, strong recommendation, low quality of evidence).

PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement (CR, Strong recommendation).

Follicle number per ovary (FNPO) ≥ 20 in at least 1 ovary should be considered the threshold for PCOM in adults (CR, Strong recommendation).

Ovarian volume (OV) ≥ 10 mL or follicle number per section (FNPS) ≥ 10 in at least 1 ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary (CR, Strong recommendation).

There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents; hence, it is not recommended in adolescents (PP).

When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM (PP).

Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥10 mL or follicle number per section (FNPS) ≥ 10 in either ovary in

adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach (PP).

In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis (PP).

Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut-off values for PCOM should be defined (PP).

There is a need for training in careful and meticulous follicle counting per ovary, and clear standardized protocols are recommended for PCOM reporting on ultrasound including at a minimum the following (PP):

- Last menstrual period (or stage of cycle).
- Transducer bandwidth frequency
- Approach/route assessed.
- Total number of 2-9 mm follicles per ovary.
- Measurements in 3 dimensions (in cm) or volume of each ovary.
- Other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥10 mm) (which should not be included in ovarian volume calculations).
- Reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted.
- Uterine features and/or pathology including endometrial thickness and pattern.

e. Anti-Müllerian hormone in the diagnosis of PCOS

Serum anti-Müllerian hormone (AMH) could be used for defining PCOM in adults (EBR, conditional recommendation, moderate quality of evidence).

Serum AMH should only be used in accordance with the diagnostic algorithm, noting that in patients with irregular menstrual cycles and hyperandrogenism, an AMH level is not necessary for PCOS diagnosis (EBR, strong recommendation, moderate quality of evidence).

We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS (EBR, strong recommendation, moderate quality of evidence).

Serum AMH should not yet be used in adolescents (EBR, strong recommendation, moderate quality of evidence).

Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed to limit over-diagnosis (PP).

Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including the following (PP):

- Age: Serum AMH generally peaks between the ages of 20-25 years in the general population.
- Body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population.
- Hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use.
- Menstrual cycle day: Serum AMH may vary across the menstrual cycle.

Laboratories involved in AMH measurements in females should use population- and assay-specific cut-offs (PP).

f. Ethnic variation

Healthcare professionals should be aware of the high prevalence of PCOS in all ethnicities and across world regions, ranging from 10% to 13% globally using the Rotterdam criteria (EBR, strong recommendation, Low quality of evidence).

Healthcare professionals should be aware that PCOS prevalence is broadly similar across world regions but may be higher in Southeast Asian and Eastern Mediterranean regions (EBR, strong recommendation, Low quality of evidence).

Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups (PP).

g. Menopause life stage

A diagnosis of PCOS could be considered as enduring/lifelong (CR, strong recommendation).

Healthcare professionals could consider that both clinical hyperandrogenism and biochemical hyperandrogenism persist in the post menopause for women with PCOS (CR, strong recommendation).

PCOS diagnosis could be considered post menopause if there is a past diagnosis, or a long-term history of oligo-amenorrhea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20-40) (CR, strong recommendation).

Further investigations should be considered to rule out androgen-secreting tumors and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe, or worsening hyperandrogenism including hirsutism (CR, strong recommendation).

h. Cardiovascular disease risk

Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in pre-menopausal women is low (EBR, conditional recommendation, Very Low quality of evidence).

All women with PCOS should be assessed for cardiovascular disease risk factors EBR, strong recommendation, Very Low quality of evidence).

All women with PCOS, regardless of age and BMI, should have a lipid profile (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels) at diagnosis. Thereafter, the frequency of measurement should be based on the presence of hyperlipidemia and additional risk factors or global cardiovascular risk (CR, strong recommendation).

All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities (CR, strong recommendation).

Funding bodies should recognize that PCOS is highly prevalent with multi-system effects including cardiometabolic disease and should diversify and increase research support accordingly (CR, strong recommendation).

Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor (CR, conditional recommendation).

Healthcare professionals, women with PCOS, and other stakeholders should all prioritize preventative strategies to reduce cardiovascular risk (CR, strong recommendation).

Consideration should be given to the differences in cardiovascular risk factors and cardiovascular disease, across ethnicities and age, when determining frequency of risk assessment (PP).

i. Impaired glucose tolerance and type 2 diabetes risk

Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes (EBR, strong recommendation, Low quality of evidence).

Glycemic status should be assessed at diagnosis in all adults and adolescents with PCOS (EBR, strong recommendation, Low quality of evidence).

Glycemic status should be reassessed every 1-3 years, based on additional individual risk factors for diabetes (CR, Strong recommendation).

Healthcare professionals, women with PCOS, and other stakeholders should prioritize preventative strategies to reduce type 2 diabetes risk (CR, Strong recommendation).

Funding bodies should recognize that PCOS is highly prevalent, has significantly higher risk for diabetes, and should be funded accordingly (CR, Strong recommendation).

Diabetes general population guidelines should consider the inclusion of PCOS as an independent risk factor for diabetes (CR, Strong recommendation).

Healthcare professionals, adults, and adolescents with PCOS and their first-degree relatives should be aware of the increased risk of diabetes and the need for regular glycemic assessment (PP).

Women with type 1 and type 2 diabetes have an increased risk of PCOS, and screening should be considered in individuals with diabetes (PP).

Glycemic testing: Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycemic status in PCOS, regardless of BMI (EBR, strong recommendation, very Low quality of evidence).

If an OGTT cannot be performed, fasting plasma glucose and/or glycated hemoglobin (HbA1c) could be considered, noting significantly reduced accuracy (EBR, conditional recommendation, very Low quality of evidence).

An OGTT should be considered in all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation (EBR, conditional recommendation, very Low quality of evidence).

Insulin resistance is a pathophysiological factor in PCOS; however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (PP).

j. Obstructive sleep apnea

Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared with women without PCOS, independent of BMI (EBR, strong recommendation, moderate quality of evidence).

Women with PCOS should be assessed for symptoms of obstructive sleep apnea (ie, snoring in combination with waking un-refreshed from sleep, daytime sleepiness, or fatigue) and if present, screen with validated tools or refer for assessment (EBR, strong recommendation, moderate quality of evidence).

Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS, noting that diagnosis requires a formal sleep study (PP).

Goals of treatment should target obstructive sleep apnea-related symptom burden (PP).

k. Endometrial hyperplasia and cancer

Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer (EBR, strong recommendation, very low quality of evidence).

Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low; therefore, routine screening is not recommended (PP).

Long-standing untreated amenorrhea, higher weight, type 2 diabetes, and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer (PP).

Women with PCOS should be informed of preventative strategies including weight management, cycle regulation, and regular progestogen therapy (PP).

When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated (PP).

l. Risks in first-degree relatives

Healthcare professionals could consider that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension (EBR, conditional recommendation, very low quality of evidence).

The cardiometabolic risk in female first-degree relatives of women with PCOS remains inconclusive (PP).

2. Prevalence, screening, and management of psychological features and models of care

Psychological features are common and an important component of PCOS that all healthcare professionals should be aware of (PP).

Funding bodies should recognize that PCOS is highly prevalent and has significantly higher psychological disorders which should be prioritized and funded accordingly (PP).

a. Quality of life

Healthcare professionals and women should recognize the adverse impact of PCOS and/or PCOS features on quality of life in adults (EBR, strong recommendation, low quality of evidence).

Women with PCOS should be asked about their perception of PCOS related-symptoms, impact on quality of life, key concerns, and priorities for management (PP).

b. Depression and anxiety

Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools (EBR, strong recommendation, high quality of evidence).

Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools (EBR, strong recommendation, high quality of evidence).

If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately, or offer treatment (CR, strong recommendation).

Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities, and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent (PP).

c. Psychosexual function

Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility, and PCOS medications (CR, conditional recommendation).

Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual functions combined with related distress (CR, strong recommendation).

d. Body image

Healthcare professionals should be aware that features of PCOS can have a negative impact on body image (EBR, strong recommendation, low quality of evidence).

e. Eating disorders

Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (EBR, conditional recommendation, low quality of evidence).

If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview. If an eating disorder or disordered eating is detected, appropriate management and support should be offered (PP).

f. Information resources, models of care, and cultural and linguistic considerations

Tailored information, education, and resources that are high quality, culturally appropriate, and inclusive should be provided to all with PCOS (EBR, strong recommendations, moderate quality of evidence).

Information, education, and resources are a high priority for patients with PCOS and should be provided in a respectful and empathic manner (EBR, strong recommendations, moderate quality of evidence).

Entities responsible for healthcare professional education should ensure that information and education on PCOS is systemically embedded at all levels of healthcare professional training to address knowledge gaps (CR, strong recommendation).

The diversity of the population should be considered when adapting practice paradigms. Healthcare professional education opportunities should be optimized at all stages of graduate and postgraduate training and continuing professional development and in practice support resources (PP).

Women should be counselled on the risk of misinformation and guided to evidence-based resources (PP).

Models of care should prioritize equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required (CR, strong recommendation).

Strategies to deliver optimal models of care could include healthcare professional education, care pathways, virtual care, broader health professional engagement (eg, nurse practitioners), and coordination tools (PP).

Public health actors should consider increasing societal awareness and education on PCOS to reduce stigma and marginalization (CR, strong recommendation).

Culturally appropriate resources and education on PCOS across the lifespan for families of those with the condition should be considered (PP).

Healthcare professionals should employ shared decision-making and support patient agency or ability to take independent actions to manage their health and care (EBR, strong recommendation, moderate quality of evidence).

The importance of being knowledgeable about PCOS; of applying evidence-based practices when sharing news on diagnosis, treatment, and health implications; and of ascertaining and focusing on patient priorities should be recognized (EBR, strong recommendation, moderate quality of evidence).

Healthcare system leaders should enable system-wide changes to support healthcare professional training, knowledge and practice in sharing news optimally, shared decision-making, and patient agency, including ensuring adequate consultation time and accessible resources (CR, strong recommendation).

Evidence-based strategies for shared decision-making and for sharing news (such as the SPIKES framework) are readily available and should be used to inform PCOS care. All healthcare professionals partnering with women with PCOS should be knowledgeable in sharing news, in shared decision-making, and in supporting patient self-management. Evidence-based strategies and resources can be used to support patient activation, which refers to modifiable knowledge, skills, ability, confidence, and willingness to self-manage one's own health and care (PP).

g. Psychological therapy

Women with PCOS diagnosed with depression, anxiety, and/or eating disorders should be offered psychological therapy guided by regional general population guidelines and the preference of the woman with PCOS (CR, strong recommendation).

Women with PCOS with disordered eating, body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction should be offered evidence-based treatments (e.g., cognitive behavioral therapy) where appropriate (CR, strong recommendation).

h. Antidepressant and anxiolytic treatment

Psychological therapy could be considered first-line management, and antidepressant medications are considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines (CR, conditional recommendation).

Lifestyle intervention and other therapies (e.g., COCP, metformin, and laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms. Where pharmacological treatment for anxiety and depression is offered in PCOS, healthcare professionals should apply caution:

- To avoid inappropriate treatment with antidepressants or anxiolytics.
- To limit use of agents that exacerbate PCOS symptoms, including weight gain.

Healthcare professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment/management (PP).

3. Lifestyle management

a. Effectiveness of lifestyle interventions

Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioral strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile (EBR, strong recommendation, very low quality of evidence).

Healthy lifestyle behaviors encompassing healthy eating and/or physical activity should be recommended in all women with PCOS to optimize general health,

quality of life, body composition, and weight management (maintaining weight, preventing weight gain, and/or modest weight loss) (CR, strong recommendation).

Healthcare professionals should be aware that lifestyle management is a core focus in PCOS management (PP).

Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS and value women's individualized preferences (PP).

There are benefits to a healthy lifestyle even in the absence of weight loss (PP).

In those with higher weight, weight management can be associated with significant clinical improvements and the following key points need to be considered including the following:

- A lifelong focus on prevention of further weight gain.
- If the goal is to achieve weight loss, a tailored energy deficit could be prescribed for women, considering individual energy requirements, body weight, and physical activity levels.
- The value of improvement in central adiposity (e.g., waist circumference and waist-hip ratio) or metabolic health.
- The need for ongoing assessment and support (PP).

Healthcare professionals should be aware of weight stigma when discussing lifestyle management with women with PCOS (PP).

Healthy lifestyle and optimal weight management, in the context of structured, intensive, and ongoing clinical support, appears equally effective in PCOS as in the general population (PP).

In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain (PP).

Insulin resistance is a pathophysiological factor in PCOS; however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (PP).

b. Behavioral strategies

Lifestyle interventions could include behavioral strategies such as goal setting, self-monitoring, problem solving, assertiveness training, reinforcing changes, and relapse prevention, to optimize weight management, healthy lifestyle, and emotional well-being in women with PCOS (CR, conditional recommendation).

Behavioral support could include goal setting, problem solving, self-monitoring and reviewing, or SMART goals (specific, measurable, achievable, realistic, and timely) (PP).

Comprehensive healthy behavioral or cognitive behavioral interventions could be considered to increase support, engagement, retention, adherence, and

maintenance of healthy lifestyle and improve health outcomes in women with PCOS (PP).

c. Dietary intervention

Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes (EBR, conditional recommendation, very low quality of evidence).

Any diet composition consistent with population guidelines for healthy eating will have health benefits and, within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals (CR, strong recommendation).

Barriers and facilitators to optimize engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimizing their diet (PP).

d. Exercise intervention

Healthcare professionals and women could consider that there is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes (EBR, conditional recommendation, very low quality of evidence).

Any physical activity consistent with population guidelines will have health benefits and, within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals (CR, strong recommendation).

Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines (PP):

- All adults should undertake physical activity as doing some physical activity is better than none.
- Adults should limit the amount of time spent being sedentary (e.g., sitting and screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.
- For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150-300 minutes of moderate-intensity activities or 75-150 minutes of vigorous-intensity aerobic activity per week or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g., resistance/flexibility) on 2 non-consecutive days per week.

- For promotion of greater health benefits including modest weight loss and prevention of weight regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate-intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g., resistance/ flexibility) ideally on 2 non-consecutive days per week.
- Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day, including activities that strengthen muscle and bone at least 3 times per week.

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure-time physical activity, transportation (eg, walking or cycling), occupational activities (ie, work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family, and community activities (PP).

Aerobic activity is best performed in bouts of at least a 10-minute duration, aiming to achieve at least 30 minutes daily on most days (PP).

Barriers and facilitators to optimize engagement and adherence to physical activity should be discussed, including psychological factors (e.g., body image concerns, fear of injury, fear of failure, and mental health), personal safety concerns, environmental factors, physical limitations, socioeconomic factors, sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered for optimizing physical activity in women with PCOS (PP).

Self-monitoring, including with fitness tracking devices and technologies for step count and exercise intensity, could be considered as an adjunct to support and promote active lifestyles and minimize sedentary behaviors (PP).

e. Factors affecting weight gain in PCOS

Healthcare professionals and women with PCOS could consider that there is a lack of consistent evidence of physiological or behavioral lifestyle differences, related to weight, in women with PCOS compared to women without PCOS (EBR, conditional recommendation, very low quality of evidence).

Whilst the specific mechanisms are unclear, it is recognized that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI which may (PP):

- Underpin greater challenges with weight management.
- Highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain.
- Assist women with PCOS and healthcare professionals in forming realistic, tailored lifestyle goals.

f. Weight stigma

Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognized (EBR, strong recommendation, low quality of evidence).

Healthcare professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS (CR, strong recommendation).

Health policy makers, managers, and educators should promote awareness of weight stigma and invest in weight stigma education and minimization strategies (CR, strong recommendation).

Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviors and health outcomes for people of all sizes. In PCOS, this includes the following (PP):

- Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only 1 indicator of health and broader factors should be assessed.
- Asking permission to discuss and measure weight and using strategies to minimize discomfort (e.g., blind weighing).
- Recognizing that the terms “overweight” and “obese/obesity” can be stigmatizing with suggested alternatives including “higher weight.”
- If weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations.
- Ensuring appropriate equipment is available for women of all sizes.
- Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences.
- Offering all women best practice assessment, treatment, and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.

Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered (PP).

4. Management of non-fertility features

a. Pharmacology treatment principles in PCOS

Shared decision-making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required (PP).

An individual's characteristics, preferences, and values must be elicited and considered when recommending any intervention alone or in combination (PP).

Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications (PP).

Medical therapy is generally not approved for use specifically in PCOS, and recommended use is therefore evidence based, but off-label. Healthcare professionals need to inform adults, adolescents, and their parents/s or guardian/ s and discuss the evidence, possible concerns, and side effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS (PP).

b. Combined oral contraceptive pills

Combined oral contraceptive pills (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles (EBR, conditional recommendation, very low quality of evidence).

The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles EBR, conditional recommendation, very low quality of evidence).

Healthcare professionals could consider that there is no clinical advantage of using high-dose ethinylestradiol (≥30 µg) versus low-dose ethinylestradiol (<30 µg) when treating hirsutism in adults with PCOS (EBR, conditional recommendation, very low quality of evidence).

General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens, or combinations of COCP cannot currently be recommended (EBR, conditional recommendation, very low quality of evidence).

The 35 µg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks (EBR, conditional recommendation, very low quality of evidence).

Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited (EBR, conditional recommendation, very low quality of evidence).

When prescribing COCPs in adults and adolescents with PCOS and adolescents at risk of PCOS (PP):

- It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies.
- Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence.
- Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 µg of ethinyl estradiol or equivalent) need consideration, balancing efficacy, metabolic risk profile, side effects, cost, and availability.
- The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines.
- The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualized discussion.
- PCOS-specific features, such as higher weight and cardiovascular risk factors, need to be considered.

c. Metformin

Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric and metabolic outcomes including insulin resistance, glucose, and lipid profiles (EBR, conditional recommendation, very low quality of evidence).

Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence (EBR, conditional recommendation, very low quality of evidence).

Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m2, acknowledging limited evidence (CR, conditional recommendation).

Where metformin is prescribed, the following need to be considered (PP):

- Shared decision-making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy.
- Mild adverse effects, including gastrointestinal side-effects, are generally dose dependent and self-limiting.
- Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations, may minimize side effects and improve adherence.
- Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents.
- Use appears safe long term, based on use in other populations; however, indications for ongoing requirement need to be considered.
- Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g., diabetes, post bariatric/metabolic surgery, pernicious anemia, and vegan diet), where monitoring should be considered.

d. Metformin and combined oral contraceptive pills

COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS (EBR, conditional recommendation, very low quality of evidence).

Metformin could be used over COCP for metabolic indications in PCOS (EBR, conditional recommendation, very low quality of evidence).

The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤ 30 kg/m2. (EBR, conditional recommendation, very low quality of evidence).

In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m2, diabetes risk factors, impaired glucose tolerance, or high-risk ethnic groups (PP).

Where COCP is contraindicated, not accepted, or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed (PP).

e. Anti-obesity pharmacological agents

Anti-obesity medications, including liraglutide, semaglutide, and both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines (CR, conditional recommendation).

Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking (PP).

Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects (PP).

Shared decision-making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side effects and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation and the lack of long-term safety data (PP).

f. Anti-androgen pharmacological agents

In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of 6 months of COCP and/or cosmetic therapy (EBR, conditional recommendation, very low quality of evidence).

Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialed, acknowledging the lack of evidence in the PCOS population (CR, conditional recommendation).

Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilization) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counselled to use effective contraception (e.g., intrauterine device or COCPs) (PP).

Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated (PP).

When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that (PP)

- Spironolactone at 25-100 mg/day appears to have lower risks of adverse effects.
- Cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma.
- Finasteride has an increased risk of liver toxicity.
- Flutamide and bicalutamide have an increased risk of severe liver toxicity.
- The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.

g. Inositol

Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism, or weight (EBR, conditional recommendation, very low quality of evidence).

Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side effects than inositol (EBR, conditional recommendation, very low quality of evidence).

Women taking inositol and other complementary therapies are encouraged to advise their healthcare professional (PP).

Specific types, doses, or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence (PP).

Shared decision-making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmacological products and doses and qualities may vary (PP).

Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared

decision-making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies (PP).

h. Mechanical laser and light therapies for hair reduction

Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety, and quality of life in women with PCOS (EBR, conditional recommendation, very low quality of evidence).

A greater number of laser treatment sessions may be required in women with PCOS, compared with women with idiopathic hirsutism, to achieve hair reduction (EBR, conditional recommendation, very low quality of evidence).

Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers (CR, conditional recommendation).

Where laser hair removal is prescribed, the following need to be considered (PP):

- Wavelength and delivery of laser treatment vary by skin and hair color.
- Laser is relatively ineffective in women with blond, grey, or white hair.
- The addition of combined oral contraceptive pills (COCP), with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone.
- Low- and high-fluence lasers appear to have similar efficacy in reducing facial hair, while low-fluence laser has reduced associated pain.

Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits (PP).

i. Bariatric/metabolic surgery

Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation, and pregnancy rates in women with PCOS (CR, conditional recommendation).

Bariatric/metabolic surgery in women with PCOS should be informed by general population guidelines (CR, strong recommendation).

PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/ metabolic surgery similarly to other metabolic conditions including diabetes (CR, conditional recommendation).

Women should be strongly counselled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after 1 year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy

complications, and prolonged hospitalization of the infant (CR, strong recommendation).

j. Pregnancy outcomes

Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support are provided (EBR, strong recommendation, very low quality of evidence).

Healthcare professionals should recognize that pregnant women with PCOS have an increased risk of the following: (EBR, strong recommendation, very low quality of evidence):

- Higher gestational weight gain
- Miscarriage.
- Gestational diabetes.
- Hypertension in pregnancy and preeclampsia.
- Intrauterine growth restriction, small for gestational age babies, and low birth weight.
- Preterm delivery.
- Caesarean section.

Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth, and caesarean section, over that observed in women without PCOS (EBR, conditional recommendation, very low quality of evidence).

Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia, and instrumental delivery (EBR, conditional recommendation, very low quality of evidence).

Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher baseline weight, excess gestational weight gain, and pregnancy complications (PP).

Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS (PP).

An OGTT should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycemia and the associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit and repeated at 24-28 weeks gestation (PP).

k. Metformin in pregnancy

Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent the following (EBR, strong recommendation, low quality of evidence):

- Gestational diabetes.
- Late miscarriage (12 weeks + 1 day to 21 weeks + 6 days gestational age)
- Hypertension in pregnancy.
- Preeclampsia.
- Macrosomia or birthweight ≥ 4000 g.

Metformin could be considered in some circumstances (eg, risk for preterm birth) to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS (EBR, conditional recommendation, low quality of evidence).

Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain (PP).

Side effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy (PP).

5. Assessment and treatment of infertility

Patients with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance (PP).

Prenatal vitamin supplementation should be commenced with ovulation induction therapy aligned to routine preconception care (PP).

Pregnancy should be excluded prior to ovulation induction therapy (PP).

The use of ovulation induction agents, including letrozole, metformin, and clomiphene citrate, is off-label in many countries. Where off-label use of ovulation induction agents is allowed, healthcare professionals need to inform women and discuss the evidence, possible concerns, and side effects (PP).

There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies, in all studies conducted with ovulation induction agents, and these should be reported in any published papers (PP).

a. Preconception risk factors

Women with PCOS should be counselled on the adverse impact of excess weight on clinical pregnancy, miscarriage, and live birth rates, following infertility treatment (EBR, strong recommendation, very low quality of evidence).

Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI > 30 kg/m2), exercise,

sleep, and mental, emotional, and sexual health should be considered and optimized to improve reproductive and pregnancy outcomes and overall health (CR, strong recommendation).

A reproductive life plan and age-appropriate education on optimizing reproductive health is recommended in adolescents and women with PCOS, including healthy lifestyle, prevention of excess weight gain, and optimizing preconception risk factors (PP).

Healthcare professionals are encouraged to seek permission and, if given, to assess weight and BMI and initiate a dialogue on the importance of weight and lifestyle on women's health before pregnancy. This requires caution to avoid weight stigma and needs to consider the cultural, social, and environmental determinants of health (PP).

Chronic conditions, such as diabetes, high blood pressure, anxiety, depression, and other mental health conditions, should be optimally managed, and women should be counselled regarding the risk of adverse pregnancy outcomes (PP).

b. Tubal patency testing

In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing, and techniques of tubal patency testing in relation to the cost and complexity of the treatment should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination (CR, conditional recommendation).

c. Letrozole

Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors (EBR, strong recommendation, high quality of evidence).

The use of letrozole is still off-label in many countries. Where it is not allowed, clinicians could use other ovulation induction agents (PP).

Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents (PP).

d. Clomiphene citrate and metformin

Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents (EBR, conditional recommendation, low quality of evidence).

Women should be counselled as to potential mild gastrointestinal side-effects with metformin (PP).

Healthcare and resource burden including monitoring, travel, and costs are lower with metformin (PP).

Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin (PP).

Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy, and live birth rates (EBR, conditional recommendation, low quality of evidence).

The risk of multiple pregnancies is increased with clomiphene citrate use (alone or in combination with metformin), and therefore, clomiphene cycles may require ultrasound monitoring (PP).

Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates (EBR, conditional recommendation, low quality of evidence).

Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates (EBR, conditional recommendation, low quality of evidence).

Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone (PP).

Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates (EBR, strong recommendation, very low quality of evidence).

Current evidence demonstrates no difference in fetal abnormality rates between letrozole or clomiphene citrate ovulation induction or natural conception (PP).

e. Gonadotrophins

Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates (EBR, conditional recommendation, low quality of evidence).

Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure and no other infertility factors (EBR, conditional recommendation, low quality of evidence).

Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors (EBR, conditional recommendation, very low quality of evidence).

Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophin (EBR, conditional recommendation, low quality of evidence).

Gonadotrophins could be second-line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction (EBR, conditional recommendation, low quality of evidence).

Where gonadotrophins are to be prescribed, the following should be considered (PP):

- Cost of the intervention for ovulation induction.
- Expertise required for the use of the intervention for ovulation induction.
- The degree of intensive ultrasound monitoring that is required.
- A low-dose step-up gonadotrophin protocol should be used to optimize the chance of mono-follicular development.
- Implications of potential multiple pregnancy.

There appears to be no difference in the clinical efficacy of the available gonadotrophin preparations (PP).

When using gonadotrophins, the best clinical practice is to avoid multiple pregnancies. Considerations here include cancelling cycles when there is more than a total of 2 follicles greater than 14 mm in diameter and advising avoidance of unprotected intercourse (PP).

Live birth rate, clinical pregnancy rate per patient, and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate (PP).

A low-dose gonadotrophin protocol should be used to optimize the chance of monofollicular growth and minimize multiple pregnancies (PP).

Cycle monitoring and drug costs coupled with multiple injections will influence the choice in gonadotrophin use (PP).

f. Laparoscopic ovarian surgery

Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors (EBR, conditional recommendation, low quality of evidence).

When using laparoscopic ovarian surgery, the following should be considered (PP):

- Comparative cost of the intervention for ovulation induction.
- Expertise required for the safe use of the intervention for ovulation induction

- Both intraoperative and postoperative risks, which are higher in women who are above healthy weight.

g. In vitro fertilization and in vitro maturation

In the absence of an absolute indication for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed (CR, conditional recommendation).

In women with anovulatory PCOS, the use of IVF is effective and when elective single-embryo transfer is used, multiple pregnancies can be minimized (PP).

Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome and options to reduce the risk should be offered (PP).

Gonadotrophin-releasing hormone (GnRH) antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate (PP).

The use of a GnRH antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome (PP).

Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos are recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of ovarian hyperstimulation syndrome (CR, strong recommendation).

Either urinary or recombinant follicle stimulating hormone (FSH) could be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation (CR, conditional recommendation).

Exogenous recombinant luteinizing hormone (LH) treatment should not be routinely used in combination with FSH therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF/ICSI (CR, weak recommendation).

Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage (EBR, conditional recommendation, low quality of evidence).

Good practice in PCOS and IVF is the use of a GnRH antagonist protocol as it gives the flexibility of using a GnRH agonist trigger, freezing all strategy to reduce the risk of ovarian hyperstimulation syndrome. However, if using a GnRH agonist long protocol, then metformin could be considered. If using metformin, the following could be considered (PP):

- Commence metformin at the start of GnRH agonist treatment.
- Gradually titrate metformin up to a dose of between 1000 and 2500 mg daily in order to minimize side effects.
- Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated.

The use of in vitro maturation (IVM) and ICSI could be considered in women with PCOS as an alternative to a stimulated IVF/ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of ovarian hyperstimulation syndrome, but a lower cumulative live birth rate (EBR, Conditional recommendation for either the option or the comparison, low quality of evidence).

The use of IVM and ICSI could be considered prior to stimulated IVF/ICSI cycles acknowledging both benefits and limitations (CR, Conditional recommendation for either the option or the comparison)

h. Inositol

Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS with infertility, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies (EBR, conditional recommendation, very low quality of evidence).

There is limited evidence with uncertain results on the effect of inositol on ovulation, clinical pregnancy, and live birth rates (PP).

Side effects and safety are not known for inositol (PP).

Women need to be aware that these agents can have limited regulation with variable dose, quality, consistency, and combination with other agents (PP).

i. Anti-obesity pharmacological agents

The recommendation to use anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish the efficacy and safety (CR).

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Menstrual Disorders report, along with their recommendations.

Table 7. List of Additional Guidelines

Additional Guidelines
Saudi Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)
Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, 2021
Premenstrual disorders: Premenstrual syndrome and premenstrual dysphoric disorder, Japan Society of Obstetrics and Gynecology, 2022
EVIDENCE-BASED MANAGEMENT OF PREMENSTRUAL DISORDERS (PMD), International Association for Premenstrual Disorders (IAPMD), 2023

1.2.1 Saudi Guideline on the Treatment of Premenstrual Dysphoric Disorder (PMDD)

PMDD is considered a disorder with substantial clinical and public health impact in a small subpopulation of menstruating women.

Due to the chronic nature of the disorder special attention should be paid to maintenance of effect and long-term safety, and the presence and acceptance of comorbidity.

The aim of this guideline is to provide guidance for the evaluation of medicinal products in the treatment of PMDD. The document was adopted from the European Medicines Agency and should be conceived as general guidance[16].

1. **Diagnostic criteria**

In the ICD-10 PMDD is mentioned as 'premenstrual tension syndrome' in the Gynecology Section.

However, Premenstrual dysphoric disorder (PMDD) has been given its own classification code and for the first time classified clearly as a gynecological, not mental, disease in the WHO's new International Classification of Diseases, ICD-11.

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, PMDD is currently categorized as a depressive illness (DSM–5).

The new DSM-5 criteria for PMDD require a combination of symptoms that began in the final week before menses, started to improve in the days after onset of menses and were absent in the postmenstrual weeks during the past year.

At least one of 5 or more required symptoms must be marked lability of affect, irritability or anger or increased interpersonal conflict, depressed mood or hopelessness or self-deprecation, or marked anxiety or tension.

Decreased interest in usual activities, subjective difficulty in concentrating, lethargy or fatigue or lack of energy, marked appetite change with overeating or food cravings, insomnia or hypersomnia, feelings of being out of control and

somatic symptoms such as bloating, weight gain, breast tenderness, and joint or muscle pain may also be present.

Table 8. DSM-5 Criteria for Premenstrual Dysphoric Disorder (Retrieved from American Psychtiatrist Association 2013[17])

DSM-5 criteria for premenstrual dysphoric disorder

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week after menses.
B. One (or more) of the following symptoms must be present: 1. Marked affective lability (eg, mood swing, feeling suddenly sad or tearful, increased sensitivity to rejection) 2. Marked irritability/anger or increased interpersonal conflicts 3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts 4. Marked anxiety, tension, and/or feelings of being keyed up or on edge
C. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from Criterion B above: 1. Decreased interest in usual activities (eg, work, school, friends, hobbies) 2. Subjective difficulty concentrating 3. Lethargy, easy fatigability, or marked lack of energy 4. Marked change in appetite, overeating, or specific food cravings 5. Hypersomnia or insomnia 6. A sense of being overwhelmed or out of control 7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of bloating, or weight gain

Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013.[7]

American College of Obstetricians and Gynecologists ACOG diagnostic criteria for PMS:

Premenstrual syndrome can be diagnosed if the patient reports at least one of the following affective and somatic symptoms during the 5 days before menses in each of the three prior menstrual cycles:

Affective:

- Depression
- Angry outbursts
- Irritability
- Anxiety
- Confusion
- Social withdrawal

Somatic:

- Breast tenderness
- Abdominal bloating
- Headache
- Swelling of extremities

These symptoms are relieved within 4 days of the onset of menses, without recurrence until at least cycle day 13.

The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use.

The symptoms occur reproducibly during two cycles of prospective recording. The patients suffer from identifiable dysfunction in social or economic performance.

2. Pathophysiology of PMDD

According to research, patients with PMDD has anomalies in the hypothalamus-pituitary-ovary axis and brain serotonergic system.

The menstrual cycle is associated with the pattern of symptoms, which include significant symptoms in the time before menses (the luteal phase), symptom remission during menstrual flow, and a symptom-free period in the follicular phase.

There have been various attempts to uncover endocrine abnormalities in people with PMDD, but It appears that ovulatory cycles are necessary for the onset of PMDD.

Research suggests that gonadal steroid levels in ovulating women with and without PMDD are similar.

Studies on PMDD tend to support the idea that women with PMDD are more sensitive to the effects of sex steroids on the brain than are women without the disorder, with abnormal hypothalamic-pituitary regulation throughout the menstrual cycle and abnormal luteal phase cortical excitability being suggested as the underlying mechanisms.

The cyclicity of symptoms diminishes during anovulatory cycles, and symptoms abate during menopause, pregnancy, or bilateral ovariectomies.

It is also likely that there is a genetic component to the existence and severity of premenstrual symptoms.

In addition, higher concordance rates are observed in monozygotic twins compared with dizygotic twins

There are risk factors associated with the development of PMDD including:

- A previous history of mood disorder.
- Genetic susceptibility,

- Premenstrual mood changes and depression.
- Past or current history of traumatic events such as sexual abuse or domestic violence
- Cigarette smoking
- Obesity

Major theories developed to explain the pathophysiology of PMDD due to ovarian hormone dysregulation.

PMDD is caused by an imbalance in the estrogen-to-progesterone ratio, with a relative progesterone deficiency.

Chronic exposure to progesterone and Allopregnanolone (progesterone metabolite) and rapid withdrawal from ovarian hormones may play a role in the etiology of PMDD.

PMDD shares many of the phenomenological features of depression and anxiety states that have been linked to serotonergic dysregulation.

Other neurotransmitter systems that have been implicated include the opioid, adrenergic, and gamma-aminobutyric acid (GABA) systems.

3. Differential diagnosis

PMDD should be separated from differential diagnostic categories including both psychiatric and nonpsychiatric disorders and physicians should be trained in handling the DSM-V criteria.

Most common psychiatric disorders that may be concurrent or exacerbated premenstrually are dysthymia, major depressive disorder (MDD), panic disorder (PD), and generalized anxiety disorder (GAD).

Less evidence exists for bipolar disorders, posttraumatic stress disorder, social phobia, eating disorders, and substance abuse.

Symptoms of endometriosis, polycystic ovary disease, adrenal system disorders and hyperprolactinemia may mimic symptoms of PMDD.

Other medical disorders that may demonstrate a premenstrual increase in symptoms include migraines, asthma, seizure disorders, irritable bowel syndrome, diabetes, chronic fatigue symptom, allergies and autoimmune disorders.

4. Treatment

Two primary treatment options have been developed based on theories about the underlying causes of PMDD:

a. Targeting the hypothalamus-pituitary-ovary axis by eliminating fluctuations in gonadal hormone levels (e.g., GnRH analogues, estradiol, combined oral contraceptives (COCs))

b. Targeting brain serotonergic synapses by increasing central serotonergic transmission (e.g., SSRI, NSRI)

Because PMDD is a cyclic, intermittent illness, both periodic and continuous treatment interventions should be considered, as they may have different effects on treatment compliance and long-term safety.

Other therapeutic approaches include pharmacological treatment of physical symptoms as well as non-pharmacological methods such as psycho-behavioral approaches, lifestyle changes, and dietary modifications, which are not addressed in this guideline.

Ideally, women with severe PMDD should be treated by a multidisciplinary team which might comprise a hospital or community gynecologist, psychiatrist or psychologist, dietitian and counsellor.

Referral to a gynecologist should be for women who have been fully evaluated as having severe PMDD and when simpler forms of therapy have been explored.

Medical Treatment of PMDD

The two chief evidence-based medical treatments of moderate to severe PMS are categorized by ovulation suppression and selective serotonin reuptake inhibitors:

Serotonin Reuptake Inhibitors: SSRIs have been proven to be effective in the treatment of severe mood and somatic symptoms of PMDD.

The ones that have been particularly linked with the relief of symptoms are Clomipramine (a tricyclic antidepressant), Selective serotonin reuptake inhibitors like escitalopram, fluoxetine, and noradrenaline reuptake inhibitor venlafaxine.

Antidepressants that predominantly affect noradrenergic transmission are not as effective for PMDD as SSRIs.

Beneficial effect of SRIs begins rapidly in PMDD whereas antidepressant effect takes several weeks.

Thus, clinicians can use SRIs intermittently from mid-cycle to menses to treat symptoms of PMDD as opposed to continuous treatment.

Side-effects of SSRIs: Nausea is the most common adverse effect, but it usually wears off in a couple of days after starting the therapy and doesn't reappear even if the therapy is intermittent. Reduced libido and anorgasmia are other common adverse effects, but they are absent in drug-free intervals.

Cognitive Behavioral Therapy: When treating women with severe PMS, cognitive behavioral therapy should be considered routinely as a treatment option.

Ovarian suppression: A number of drugs are capable of performing this function, but they are not without their own side-effects which may influence the efficacy of the treatment or the duration for which they may be given.

Combined oral contraceptive pill: Although widely used in clinical practice, their efficacy in treating PMDD has not been strongly supported by evidence.

Women on OCP experience more hormone-related symptoms on hormone-free days and hence OCP treatment with fewer hormone-free days might be beneficial.

Newer contraceptive pill types may represent effective treatment for PMDD and should be considered as one of the first-line pharmaceutical interventions of these women.

Transdermal estradiol: transdermal (patch) 17β estradiol combined with cyclical progestogen is effective for the management of physical and psychological symptoms of severe PMDD.

Implants are less commonly used for PMDD since patches have become available due to their long-lasting effects.

Additional barrier or intrauterine methods of contraception should be used when estradiol (patches and implant) are used in PMS as ovulation suppression cannot be guaranteed.

There are insufficient data to confirm long-term endometrial and breast safety because long-term randomized prospective safety studies are lacking.

Percutaneous estradiol, either as an implant or as a patch, combined with cyclical progestogen, has been shown to be effective for the management of physical and psychological symptoms of severe PMDD.

Progestogen intolerance: Use of continuous estradiol normally necessitates the addition of cyclical progestogen (10 - 12 days) to avoid endometrial build-up in women who have a uterus.

The progestogen releasing system (Mirena) can maximize efficacy by minimizing PMS-like adverse effects.

Even the low systemic levels of levonorgestrel released by the Mirena, can initially produce PMS-type adverse effects in the progestogen intolerant woman.

It might still be of advantage to use a Mirena or vaginal progesterone (Cyclogest pessaries or Crinone gel 8% – not licensed for this indication) in the progestogen intolerant woman.

Treatment with the lowest possible dose of progestogen is recommended to minimise adverse effects.

Danazol: Cycle suppression may be achieved using Danazol, an androgenic steroid.

Due to masculinizing side-effects, especially at higher, cycle-suppressing doses, it is not commonly used.

Gonadotrophin releasing hormone (GnRH) analogues HS: GnRH analogues have been very successfully employed for many years to suppress ovarian steroid production.

Prolonged use should be retained for women with the most severe symptoms.

Data show that symptoms due to the hypoestrogenic state can be virtually eliminated and bone mineral density can be maintained by the use of HRT. Continuous combined therapy is preferable to sequential combined therapy in order to minimize the risks of symptom re-appearance of PMS-like progestogenic effects.

When treating women with PMDD, with GnRHa therapy, treatment should only be continued for 6 months when used alone.

Treatment should be combined with HRT to reduce bone density loss.

Women on long- term treatment should have annual measurement of bone mineral density (ideally by dual energy X-ray absorptiometry).

Treatment should be stopped if bone density declines significantly in scans performed one year apart.

General advice about how exercise, diet and smoking affect bone mineral density should be given.

Surgical Treatment of PMDD

Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the ultimate form of ovulation suppression and the only true cure for PMDD as this removes the ovarian cycle completely.

The procedure is only rarely performed for this indication, as a lesser alternative can usually be found.

When treating women with PMDD, surgery should not be contemplated without preoperative use of GnRH analogues as a test of cure and to ensure that HRT is tolerated.

Such therapy should be reserved for sufferers of extremely severe PMS in whom other treatment has failed.

COMPLEMENTARY THERAPIES (CAMs)

It is difficult to assess the true value of most of these therapeutic interventions because they are freely available without prescription or physician recommendation, and with little regulation of efficacy or safety.

Most are not licensed or registered for the treatment of PMS.

Magnesium: there is some evidence that regular use of magnesium supplements is of benefit in managing premenstrual syndrome. However, more data would be desirable.

Calcium / Vitamin D: studies suggest that blood calcium and Vitamin D levels are lower in women with PMDD and that calcium supplementation may reduce symptom severity, but it is unknown whether this may prevent the initial development of PMS.

Agnus Castus: the fruits of Vitex agnus castes (The chaste tree) contain a mixture of iridoids and flavonoids. The mechanism of action may be related to modulation of stress induced prolactin secretion via dopamine without directly affecting lutenising or follicle stimulating hormones.

1.2.2 Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin (2021)

Uterine leiomyomas are solid neoplasms composed of smooth muscle cells and fibroblasts.

Leiomyomas vary in size and location. A standardized leiomyoma subclassification system was developed by the International Federation of Gynecology and Obstetrics (FIGO) to describe uterine leiomyoma location in relation to the endometrial and serosal surfaces.

The purpose of this Practice Bulletin is to provide updated evidence-based recommendations for the medical, procedural, and surgical management of symptomatic leiomyomas[18].

1. **Symptoms**

Prolonged or heavy menstrual bleeding, with or without anemia, and the sequelae of uterine enlargement are the most common presenting symptoms of patients with uterine leiomyomas.

Pelvic pressure, urinary frequency, and constipation also can result from the presence of large leiomyomas within the pelvis and are collectively referred to as bulk symptoms.

2. **Diagnosis**

Clinical evaluation for suspected leiomyomas begins with a complete medical history and an abdominal and pelvic examination.

Transvaginal ultrasonography is useful as a screening test to assess for leiomyomas.

Sono-hysterography is useful to identify and distinguish between type 0, type 1, and type 2 leiomyomas, in which the percentage of submucosal component varies.

Hysteroscopy is useful to distinguish between type 2 and type 3 leiomyomas, in which there is contact with the endometrium but there may not be distortion of the endometrial cavity.

Magnetic resonance imaging can be useful in surgical planning, determining vascularity and degeneration, and distinguishing between type 4 and type 5 leiomyomas, in which there is an intramural component, with or without a submucosal component.

3. Treatment Options

There are a variety of treatment options for leiomyomas, including expectant, medical, interventional, and surgical therapies.

When considering treatment options, patient-specific symptoms and severity should be addressed.

If a patient describes symptoms that are neither severe, nor debilitating, expectant management may be appropriate.

Medical treatments primarily address bleeding symptoms. Procedural interventions and surgical approaches treat bulk symptoms by decreasing uterine mass.

There is evidence to suggest that nonsteroidal anti-inflammatory drugs are associated with modest improvement in heavy menstrual bleeding but there is no evidence for their use specifically for the treatment of Abnormal uterine bleeding associated with leiomyomas (AUBL).

Complementary and alternative medicines, including acupuncture and herbal preparations, are used by many patients to treat uterine leiomyomas; however, there is a lack of evidence to support their efficacy.

Patients should be counseled on all treatment options that are available and accessible, with a discussion of the risks and benefits of the various treatment options to guide patient counseling and shared decision making.

Clinical Considerations and Recommendations

Expectant management of uterine leiomyomas can be considered for patients who are asymptomatic or for those who do not desire intervention.

Patients should be counseled to return for follow up if symptoms become bothersome or if active management or pregnancy is desired.

Medical treatment options for uterine leiomyomas include agents that address only

- Bleeding symptoms: gonadotropin releasing hormone [GnRH] antagonists, levonorgestrel releasing intrauterine devices [LNG-IUDs], contraceptive steroids, and tranexamic acid
- And medications that reduce both bleeding and leiomyoma size: GnRH agonists and selective progesterone receptor modulators

Some medical therapies for uterine leiomyomas are indicated for long term use, whereas others are meant to be a bridge to surgical treatments, interventional procedures, or menopause.

Because there is insufficient comparative evidence to guide recommendations on first-line medical therapy, decisions should be guided by an individual patient's symptoms and treatment goals.

Gonadotropin-Releasing Hormone Antagonists with Hormonal AddBack Therapy

Oral GnRH antagonist with hormonal add-back therapy can be considered for the treatment of AUB-L for up to 2 years.

Elagolix is an oral gonadotropin releasing hormone antagonist that results in reversible, dose-dependent, suppression of gonadotropins and ovarian sex hormones.

The combination of elagolix (300 mg twice daily) with add-back therapy (1 mg estradiol and 0.5 mg norethindrone acetate once daily) is U.S. Food and Drug Administration (FDA)-approved for up to 24 months of use to treat heavy menstrual bleeding associated with uterine leiomyomas (ie, AUB-L).

The hormonal add-back therapy is indicated to offset the hypoestrogenic effects of elagolix, including hot flushes, increased mean serum lipid levels, and bone mineral density loss.

Data on a second oral GnRH antagonist, **relugolix**, combined with hormonal add-back therapy as a once daily relugolix combination therapy shows similar improvement in heavy menstrual bleeding as elagolix with add-back hormone therapy as well as similar adverse effects.

Levonorgestrel-Releasing Intrauterine Devices

A 52-mg Levonorgestrel-releasing intrauterine devices (LNG-IUD) can be considered for the treatment of AUB-L.

LNG-IUD can reduce menstrual bleeding by inducing endometrial decidualization and atrophy and have been found to decrease heavy menstrual bleeding in patients both with and without leiomyomas.

There is insufficient evidence to support the use of an LNG-IUD for the treatment of uterine leiomyoma symptoms other than bleeding.

Contraceptive Steroid Hormones

Among patients with heavy menstrual bleeding without uterine leiomyomas, combined hormonal contraceptive and progestin-only pills reduce menstrual blood loss and are considered a reasonable option for initial treatment.

Combined and progestin-only hormonal contraceptives are a reasonable option to consider in the treatment of heavy menstrual bleeding in patients with uterine leiomyomas, although there are limited direct data to support their effectiveness.

There is no evidence to support the use of contraceptive steroid hormones to manage bulk symptoms associated with uterine leiomyomas.

Tranexamic Acid

Tranexamic acid can be considered for the treatment of AUB-L.

Tranexamic acid is an antifibrinolytic medication that prevents fibrin degradation, and it is an effective treatment for heavy menstrual bleeding.

Limited data also show that tranexamic acid is associated with a statistically significant decrease in AUB-L.

MEDICAL THERAPIES FOR BLEEDING SYMPTOMS AND UTERINE ENLARGEMENT

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists, either with or without add-back hormonal therapy, are recommended for the short-term treatment of AUB-L and uterine enlargement associated with uterine leiomyomas and as a bridge to other treatment strategies.

GnRH agonists induce hypogonadism, which causes a reduction in menstrual bleeding that often results in amenorrhea.

Use of a GnRH agonist is a short-term management strategy that is meant to bridge treatment to interventional procedures, surgical management, menopause, or other medical therapies.

Treatment with GnRH agonists is associated with reduction in leiomyoma size and overall size of the uterus, decreased AUB-L and dysmenorrhea, and improvement in quality-of-life measures.

Leiomyoma regrowth, often back to pretreatment levels, is observed between 3 and 9 months after cessation of treatment, which explains why it is primarily used as a bridge therapy.

There is a lack of long-term follow-up data regarding maintenance of treatment effects on menstrual bleeding and pain.

GnRH agonists often are used to reduce uterine volume before surgical therapy, which may facilitate the use of a minimally invasive surgical route, allow for a smaller incision, or enable the use of an incision type associated with decreased morbidity.

Concomitant therapy with low-dose estrogen or progestin, or both, may mitigate the hypoestrogenic adverse effects of GnRH agonists, which include menopausal symptoms, unfavorable changes in lipid profile, and a decrease in bone density.

The type, dose, and route of delivery for add-back therapy varies depending on patient preference and the severity of symptoms, but a regimen of oral conjugated estrogen 0.625 mg and norethindrone acetate 2.5–5.0 mg daily is commonly used.

Because of the risk of long-term hypoestrogenic adverse effects, treatment with GnRH agonists typically is limited to 6 months without add-back therapy and 12 months with add-back therapy.

Selective Progesterone Receptor Modulators

Mifepristone and ulipristal acetate exhibit efficacy in the short-term treatment of AUB and uterine enlargement associated with uterine leiomyomas,

Yet currently they are not approved in the United States for the treatment of leiomyomas.

Ulipristal acetate is approved outside the United States, but post-marketing reports of rare but serious liver injury, including need for liver transplantation, have prompted the European Medicines Agency and other regulatory agencies to significantly limit the use of daily ulipristal acetate for leiomyoma treatment.

Uterine Artery Embolization

Uterine artery embolization (UAE) is recommended as an interventional procedure for the treatment of uterine leiomyomas in patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes.

Uterine artery embolization is consistently associated with a significant reduction in leiomyoma and uterine volume that is maintained for up to 5 years based on long-term follow-up data.

Radiofrequency Ablation

Laparoscopic radiofrequency ablation can be considered as a minimally invasive treatment option for the management of symptomatic leiomyomas in patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes.

Focused Ultrasound

Focused ultrasound surgery, guided by diagnostic ultrasound or magnetic resonance, is a noninvasive treatment modality that uses multiple high-intensity ultrasound waves to cause coagulative necrosis of uterine leiomyomas.

Endometrial Ablation

Limited data suggest that AUB-L is improved with endometrial ablation and is maintained in the year following ablation.

However, there is insufficient evidence to make a clinical recommendation regarding the use of endometrial ablation for the treatment of uterine leiomyomas.

Benefits and risks of surgical management for uterine leiomyomas

Surgical treatment options for uterine leiomyomas include myomectomy and hysterectomy.

Goals of treatment should be defined for each patient, including desire for uterine preservation and future fertility, as well as primary symptomatology, including bleeding and bulk symptoms.

The most minimally invasive route is recommended whenever feasible.

Gonadotropin-releasing hormone agonists are often used to reduce uterine volume before surgical therapy.

However, if the specimen or uterus is too large to be removed intact, or there is not a surgical orifice for intact specimen removal, such as with laparoscopic myomectomy, morcellation is required.

Preoperative Anemia

Preoperative anemia is associated with a higher risk of perioperative blood transfusion and may result in increased operative morbidity and mortality.

Myomectomy

Myomectomy is recommended as a surgical management option for symptomatic leiomyomas in patients who desire uterine preservation or future pregnancy and are counseled about the risk of recurrence.

Myomectomy is a uterine sparing treatment option that removes accessible leiomyomas, which allows for future pregnancy.

Hysterectomy

Hysterectomy is recommended as a definitive surgical management option for the treatment of AUB-L and bulk symptoms associated with uterine leiomyomas in patients who do not desire future childbearing or do not wish to retain their uterus and are counseled about the long-term health risks.

1.2.3 Premenstrual Disorders: Premenstrual Syndrome and Premenstrual Dysphoric Disorder, Japan Society of Obstetrics and Gynecology (2022)

Premenstrual symptoms are characterized by a variety of psycho-physical symptoms that are present in the luteal phase before menstruation and impair the quality of life of many women.

As diseases with intense premenstrual symptoms, they have been classified as premenstrual syndrome (PMS) in the field of gynecology and as premenstrual dysphoric disorder (PMDD) in the field of psychiatry.

In recent years, they have been recognized under the name of premenstrual disorders (PMDs), which encompasses both.

In this review, we will examine the current status and challenges of diagnosis and treatment in PMDs[2].

1. Diagnostic criteria

The American College of Obstetricians and Gynecologists (ACOG)'s PMS diagnostic criteria require one or more affective or somatic symptoms that impair social, work, or school performance for a diagnosis of PMS.

PMDD is diagnosed mainly by its psychiatric symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM).

According to these criteria, at least five symptoms including affective symptoms with functional impairment are necessary for diagnosis. In actual clinical practice, premenstrual symptoms may indicate severe impairment of social life, although they do not meet the diagnostic criteria for PMDD.

In contrast, the diagnostic criteria for PMD proposed by International Society for Premenstrual Disorders (ISPMD) have no restrictions regarding the number of symptoms and match the needs of patients seeking treatment.

Patients tend to overestimate premenstrual symptoms because they are cyclic, present only in the luteal phase, and resolve after the onset of menstruation.

Therefore, each of the diagnostic criteria of ACOG, DSM, and ISPMD also requires the inclusion of a symptom diary for two cycles of a prospective menstrual cycle.

Screening and diagnostic questionnaires

Prospective two menstrual cycle symptom record is necessary for accurate diagnosis, but it is also complicated.

The Premenstrual symptom screening tool (PSST) is a screening tool originated from the DSM-IV PMDD criteria.

The PSST consists of 12 symptoms listed in the DSM-IV criteria for PMDD, with "Insomnia or hypersomnia" divided into "Insomnia" and "Hypersomnia" as separate symptoms. It also includes five items on functional impairment; in total, 17 items are included in the PSST.

PSQ is a screening tool developed in Japan independently of the PSST, and consists of 14 items in total, including 11 premenstrual symptoms listed in the DSM-IV criteria and three items to evaluate the degree of social disability caused by these symptoms.

After interview and use of a validated screening tool, an accurate diagnosis requires a prospective symptom assessment of two menstrual cycles.

The Diary Record of Severity of Problems (DRSP) is the most universally used diary for recording symptoms, based on the DSM-IV PMDD criteria, worldwide, and is included in the UK's Green Top Guidelines.

2. Etiology

Although the precise etiology of PMDs is remains unknown, there is no doubt about the involvement of hormonal fluctuations, as symptoms do not appear before menarche, during pregnancy, or after menopause.

In PMDD patients, the administration of leuprolide, a Gonadotropin-releasing hormones (GnRH) agonists, which suppresses ovulation, suppresses premenstrual symptoms, but estrogen and progesterone replacement has been reported to cause a recurrence of premenstrual symptoms.

Two neurotransmitters have been proposed to be involved in the pathology of PMDs: serotonin and γ-amino butyric acid (GABA).

- Serotonin is activated by estrogen, so serotonin levels are physiologically low before menstruation.
- Several reports using neuro-imaging showed some relationships between PMDD and GABAergic system in brain.

3. Treatments

Five types of treatments are used including: nonpharmacologic, antidepressants, hormone therapy, vitamin and complementary medicine, and surgery.

a. Nonpharmacologic treatments

It is a good alternative when symptoms are mild, or when premenstrual symptoms are present but do not meet the diagnostic criteria for PMS or PMDD.

Because it is less invasive, it is positioned as the first step in treatment.

CBT group showed a significantly lower recurrence rate during follow-up.

With regard to lifestyle improvements, better eating habits and adequate exercise will be adopted.

Dietary intervention with complex carbohydrates (elevating serum tryptophan) in the luteal phase improved PMS mood and appetite symptoms.

b. Antidepressants

There is strong evidence for the use of SSRIs for the treatment of PMDD75 and they are considered a first line of treatment.

Unlike the treatment of depression, the efficacy of SSRIs administered after the onset of symptoms has been reported in the case of PMDD, assuming a different mechanism of action.

c. Hormone therapy

The purpose of hormonal treatment is to suppress ovulation.

Oral contraceptives (OCPs) were the first drugs to be used.

OCPs containing drospirenone and ethinyl estradiol significantly improved PMDD symptoms.

Continuous dosing regimens are advantageous for improving premenstrual symptoms because they eliminate the hormone-free period compared with regimens with classical withdrawal periods.

There are reports suggesting the effectiveness of sequential dosing.

GnRH agonists suppress ovulation and improve the PMS symptoms.

Low estrogen status results in symptoms of vasomotor symptoms, bone loss, and vaginal atrophy, similar to those seen after menopause, requiring estrogen add-back.

Because of this invasive nature of the treatment, GnRH agonists are not first-line drugs and are indicated for SSRIs and OCPs invalid cases.

d. Vitamins and complementary medicine

A variety of alternative medicines are being used around the world, but the evidence is limited.

Vitamin B6 (pyridoxine) has been extensively studied and moderate benefit was reported in 100 mg of pyridoxine treatment for premenstrual symptoms. In

Calcium carbonate supplementation with 1200 mg daily was reported to be effective compared with placebo for premenstrual symptoms.

Vitex agnus castus (chasteberry) is widely used in Europe and has been the subject of numerous studies reporting efficacy compared with placebo.

In Japan, Kampo, a type of herbal medicine, has traditionally been used in general practice.

e. Surgery

Surgical intervention, total hysterectomy and bilateral adnexectomy, is a permanent treatment limited to cases of recurrence of intense symptoms.

EXPECTED NEW TREATMENTS

The Allopregnanolone (ALLO) targeting strategy, such as a 5-alpha reductase inhibitor (Dutasteride) and ALLO antagonist (Sepranolone) are promising.

Ulipristal Acetate (UPA), a progesterone receptor modulator, which functions as a progesterone antagonist, has been shown to be effective for PMDD symptoms by double-blind, placebo-controlled, randomized, comparative studies.

Vitamin B6 consists of three forms, pyridoxine, pyridoxal, and pyridoxamine. Among them only pyridoxamine has an amino group and is characterized by the fact that it acts with reactive carbonyl compounds (RCOs) to eliminate their action.

RCOs act to degrade serotonin and GABA, thus pyridoxamine may help maintain these brain transmitters by removing the effects of RCOs. It also acts to promote the synthesis of serotonin and GABA.

Pyridoxamine would be more effective than pyridoxine for the treatment of premenstrual symptoms.

1.2.4 Evidence-Based Management of Premenstrual Disorders (PMD), International Association for Premenstrual Disorders (IAPMD) (2023)

Premenstrual Disorders such as Premenstrual Dysphoric Disorder (PMDD) and Premenstrual Exacerbation (PME) of psychiatric disorders are complex to diagnose and treat. The document below provides guidelines to help healthcare providers educate and treat their patients effectively[19].

1. **Assessment and diagnosis of PMD**

To confirm the diagnosis, two months of daily symptom ratings are recommended to differentiate between PMDD (symptoms present only premenstrually), PME (symptoms always present but worsened premenstrually), and non-cyclical symptoms.

Daily ratings can also be continued in the context of treatment to evaluate effectiveness over time.

2. **Treatment of PMD**

Several treatments have been found to be effective, and more are currently under investigation. Nearly all clinical trials in this area have focused on PMDD. Tables 9, 10, and 11 are organized according to effectiveness and safety of treatments for PMD.

Table 9. Treatments with Strong Scientific Evidence for Efficacy and Safety in PMDD

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY
Selective serotonin reuptake Inhibitors (SSRIs) - fluoxetine 20mg ("Prozac") - sertraline 50-150mg ("Zoloft") - paroxetine 20-30mg ("Paxil") - citalopram 20-30mg ("Celexa") - escitalopram 10-20mg ("Lexapro")	Strong evidence of efficacy for PMDD in many trials. Response rates in randomized controlled trials are around 60%. SSRIs tend to have a rapid effect, often performing better than placebo after just one day.	Strong evidence of efficacy for PMDD in many trials. Response rates in randomized controlled trials are around 60%. SSRIs tend to have a rapid effect, often performing better than placebo after just one day.	Well tolerated in general, but side effects are common. Most frequent side effects are nausea, low energy, sleepiness, and decreased libido.

Dosing Schedule: Symptom-Onset, Luteal, or Continuous			
Drospirenone-containing oral Contraceptive pill with Shortened hormone-free Interval Drospirenone 3mg/ ethinylestradiol .02mg daily (e.g., "Yaz") Dosing: 24-4 or continuous dosing (i.e., shortened or eliminated hormone-free interval)	Evidence of efficacy for PMDD from two randomized controlled trials. Usually effective in first month of treatment. Response rates were 48% and 61%. Effects may be smaller than SSRIs.	One study shows no benefit for PME of depressive disorders when given as an adjunctive treatment to SSRI.	Well tolerated, generally few side effects. Risk of blood clot and estrogen dependent cancers should be considered based on individual risk profiles. Some individuals do not tolerate progestins and develop chronic symptoms similar to PMDD; progestin treatment should be discontinued in these patients.
Gnrh analogues **Dosing: Monthly outpatient injections** **- leuprolide 3.75mg monthly injection ("Lupron")** **- goserelin 3.6mg monthly** Injection ("Zoladex")	Many trials demonstrate effectiveness for severe PMDD. Typically reserved for those who have failed to respond to both SSRI and OCs. Not effective when ovulation is not suppressed.	Two studies show no benefit for subsamples with PME of depressive disorders. However, no evidence is available regarding effectiveness when long-term hormone addback is provided Note: If PME (e.g., of depression) is comorbid with other symptoms (e.g., anxiety, irritability) that DO show a PMDD-like confinement to the luteal phase, treatment may still be indicated for PMDD.	Menopausal symptoms. Requires Suppression of ovulation and hormone replacement to prevent related hormone flux bone loss.

Gnrh analogues + stable Hormone addback - transdermal estradiol addback ("Climara") - progestogen addback for endometrial protection ("Prometrium")	Many trials demonstrate effectiveness for severe PMDD. Typically reserved for those who have failed to respond to both SSRI and OCs.	Untested for PME of depressive disorders, but represents a rational option to trial for treatment-resistant patients. Note: If PME (e.g., of depression) is comorbid with other symptoms (e.g., anxiety, irritability) that DO show a PMDD-like confinement to the luteal phase, treatment may be indicated for PMDD.	In two studies, the first month of stable oral estrogen + vaginal progesterone addback caused a resurgence of PMDD symptoms, but symptoms remitted after 1 month. Patients should be informed of possible short-term symptom flare and appropriate supports should be provided.
Total hysterectomy with Bilateral salpingooophorectomy (thbso) **-** removal of both ovaries is required - removal of uterus is indicated to eliminate need for progestin addback post-surgery	Studies indicate that THBSO is Untested, but a rational effective for those patients who treatment choice for a patient improves during GnRH agonist who has improved during GnRH trial. agonist trial. If patient does not tolerate GnRH analogues (and therefore cannot get a "fair GnRH trial"), THBSO may still be indicated given may still be indicated given evidence of severe cyclicity.	Untested, but a rational treatment choice for a patient who has improved during GnRH agonist trial. If patient does not tolerate GnRH analogues (and Therefore, cannot get a "fair GnRH trial"), THBSO may still be indicated given evidence of severe cyclicity.	A very routine and safe gynecologic procedure, but still major abdominal surgery with risks (including bleeding, infection, and death). Risk increases with other medical conditions (heart, lung, liver, or kidney disease, obesity, diabetes, history of prior surgery). Permanent. Requires hormone replacement to prevent bone loss.
Cognitive-behavioral Therapies Dosing: Weekly sessions with a qualified therapist with appropriate	CBT is a useful tool for reducing functional impairment related to emotional symptoms across disorders, and some evidence	Untested for PME of psychiatric disorders but is a rational treatment choice given the widespread	Well tolerated, generally few side effects when provided by a qualified professional.

training in CBT and DBT. **- Cognitive Behavioral Therapy (CBT)** **- Dialectical Behavior Therapy (DBT)** **Close attention should be paid to the quality of the therapy being provided; providers not engaging in skills training or providing behavioral homework assignments to patients** should be replaced with providers more adherent to CBT principles	suggests it may be supportive for patients with PMDD specifically. DBT is effective for preventing suicidal behaviors, a common outcome in severe cases of PMDD.	effectiveness of CBT for psychiatric disorders.	

Table 10. Treatments with Limited but Promising Scientific Evidence for Efficacy and Safety in PMDD

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY
5-alpha reductase inhibitors - dutasteride 2.5mg/day ("Avodart") Note: finasteride is untested in clinical trials but is sometimes used in clinical practice due to its shorter half-life, which may reduce the risk of birth defects in the event of pregnancy.	One study shows improvement in PMDD symptoms with dutasteride; dosage must be high enough to inhibit formation of allopregnanolone.	Untested for PME of psychiatric disorders. Given evidence of reduced biosynthesis of GABAergic neurosteroids (e.g., allopregnanolone) in chronic depressive and anxiety disorders, this medication is not recommended for PME of psychiatric disorders as it may further exacerbate neurosteroid deficits.	Causes birth defects if conception occurs while on the drug; a period of washout is needed prior to pregnancy to avoid birth defects. Patients should be monitored closely for side effects since no long-term trials exist in PMDD. In other populations, these medications can cause depression.

Ovulation suppression using transdermal estradiol + cyclical progestogen .1mg Transdermal E2 Patch (twice weekly; "Vivelle") + norethisterone 1mg/day, 10 days per cycle18 Alternative Progestogen for Endometrial Protection: - levonorgestrel-containing IUD ("Mirena")	There have been two positive trials. May represent alternative to OCs for those who cannot tolerate synthetic progestins if anovulation can be achieved at safe doses. More work is needed to determine the safety and efficacy of various doses.	Not tested	Increased risk of blood clots, increased breast cancer risk, and increased endometrial thickening/cancer risk can occur in at-risk women, particularly with inadequate progestogen opposition.
Quetiapine (luteal phase; Adjunct to SSRI) - 25mg quetiapine/day during the luteal phase ("Seroquel")	One small trial demonstrated benefit as an adjunctive treatment to SSRI.	Not tested	Generally safe and well tolerated, but potential for serious and life-threatening side effects.

Table 11. Treatments with No Evidence, Mixed Evidence, or Negative Evidence for Efficacy in PMDD

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY
Lifestyle changes **- Improved diet** **- Increased exercise** **- Reduced caffeine intake** - Reduced alcohol intake	A healthy lifestyle improves general mental and physical health. However, only low-quality evidence is available linking these outcomes to premenstrual symptoms, and findings are mixed. May be more appropriate		

	for mild premenstrual symptoms than for PMDD.		
Vitamin and mineral Supplements	Mixed evidence. May be more appropriate for mild premenstrual symptoms than for PMDD. Some evidence that calcium, magnesium, Vit D, and Vit B6 supplements may improve premenstrual symptoms.	Not tested	Supplements are readily available, but also poorly regulated in the United States. Risk of overdose or toxicity. Very safe if taken in consultation with a provider.
Levonorgestrel containing Continuous Oral contraceptive pill - levonorgestrel .09mg + .02mg ethinylestradiol daily with no pill free interval ("Lybrel")	Four studies show inconsistent effects in PMDD, with some demonstrating benefit and others not.	Not tested	Risk of blood clot and Prevention of ovulation. estrogen-dependent cancers should be considered based on individual risk profiles. Some individuals do not tolerate oral contraceptives and develop chronic or cyclical symptoms similar to PMDD; progestin containing medications should be discontinued for these patients.
Combined EE + progestin Vaginal ring contraceptive Ring **("Nuvaring")**	Not yet tested, but is known to consistently suppress ovulation and may be a rational Treatment given efficacy of other ovulation-suppression agents in PMDD; however, patient should be monitored	Not tested. Given the lack of efficacy of other ovulation-inhibiting agents in PME of depression, a beneficial effect is not necessarily expected.	Risk of blood clot and estrogen-dependent cancers should be considered based on individual risk profiles. Can be easily removed by patient.

	for progestin-induced mood symptoms.		
Levonorgestrel-containing Intrauterine device (IUD) ("Mirena", "Skyla")	No evidence available, but not a rational treatment given that they do NOT consistently suppress ovulation.	No evidence, but not a rational treatment given that they do NOT consistently suppress ovulation	May have adverse effects on physiological stress responses; many women discontinue due to depressive symptoms.
COPPER IUD ("Paragard")	No evidence available, but not a rational treatment given its inability to suppress ovulation	No evidence, but not a rational treatment given its inability to suppress ovulation.	Heavy period
DANAZOL ("Danocrine")	Not effective for emotional PMDD symptoms when considering the whole cycle.	Not tested. Not recommended given side effect profile.	Common side effects include acne, weight gain, hirsutism, deepening of the voice; some changes may be irreversible. May cause birth defects.
BENZODIAZEPINES - alprazolam ("Xanax")	Mixed evidence, with well controlled studies showing either no benefit or some benefit. Tolerance and reduced efficacy expected with long-term use. Not indicated for those with marked impulsivity or family/personal history of drug abuse. Not indicated for daily or long-term use.	Not tested	High risk of addiction and abuse; indicated for those with marked tolerance often develops. Withdrawal can be life-threatening.
Oral micronized progesterone Or progestins only. - usually given in the luteal phase only	Several studies show that this is ineffective, and is likely to worsen symptoms in the first month.	Not tested	Progestins can trigger mood symptoms, particularly acutely.

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs SFDA registered, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by FDA and/or EMA but are not yet SFDA registered.

2.1 Additions

There have been no new drugs SFDA approved for menstrual disorders.

2.2 Modifications

There are no new modifications regarding the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

Hydroxyprogesterone was withdrawn from Saudi FDA.

2.4 Other Drugs

Several drugs are under review for PMDD management. The Allopregnanolone (ALLO) targeting strategy, such as a 5-alpha reductase inhibitor (Dutasteride) and ALLO antagonist (Sepranolone) are promising. At the same time, Ulipristal Acetate, a progesterone receptor modulator, has been shown to be effective for PMDD symptoms. Yet, none of the above medication granted FDA approval yet for this indication.

ORIAHNN®, the combination of elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, was approved by FDA in 2020 indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. A similar combination, Myfembree® (relugolix, estradiol, and norethindrone acetate), approved by FDA in May of 2021 for the management of heavy menstrual bleeding associated with uterine fibroids premenopausal women and in August of 2022 for the management of moderate to severe pain associated with endometriosis in premenopausal women.

2.4.1 Myfembree® (Relugolix, Estradiol, and Norethindrone Acetate)

MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, approved by the

FDA in 2021 and indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Main characteristics are listed in the table below:

Table 12. Myfembree® Drug Information

MYFEMBREE® (RELUGOLIX, ESTRADIOL, AND NORETHINDRONE ACETATE)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2021
EMA	Yes, 2021
MHRA	No
PMDA	No
Indication (ICD-10)	D25.9
Drug Class	Gonadotropin-releasing hormone (GnRH) receptor antagonist, estrogen, and a progestin combination
Drug Sub-class	-
ATC Code	-
Pharmacological Class (ASHP)	Gonadotropin-releasing hormone (GnRH) receptor antagonist, estrogen, and a progestin combination
DRUG INFORMATION	
Dosage Form	**Tablet: fixed-dose combination containing Relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg.**
Route of Administration	Oral use

Dose (Adult) [DDD]*	- Exclude pregnancy and discontinue hormonal contraceptives prior to MYFEMBREE initiation· - Take one tablet orally once daily· - Take the missed dose of MYFEMBREE as soon as possible the same day and then resume regular dosing the next day at the usual time· - If concomitant use of oral P-gp inhibitors is unavoidable, take MYFEMBREE at least 6 hours before taking the P-gp inhibitor. - Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible.
Maximum Daily Dose Adults*	One tablet per day
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	
Prescribing edits*	AGE, G
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): Approved for use in adult females.	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reactions (incidence ≥ 3%) are hot flush, hyperhidrosis or night sweats, uterine bleeding, alopecia, and decreased libido.
Drug Interactions*	Avoid use of MYFEMBREE with oral P-gp inhibitors.

	Avoid use with combined P-gp and strong CYP3A inducers, as the exposure of the components of MYFEMBREE may be decreased.
Special Population	Lactation: Advise women not to breastfeed while taking MYFEMBREE
Pregnancy	Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE and discontinue treatment if pregnancy is confirmed.
Lactation	Advise not to breastfeed.
Contraindications	• High risk of arterial, venous thrombotic, or thromboembolic disorder • Pregnancy • Known osteoporosis • Current or history of breast cancer or other hormone-sensitive malignancies • Known hepatic impairment or disease • Undiagnosed abnormal uterine bleeding • Known hypersensitivity to components of MYFEMBREE.
Monitoring Requirements	• Thromboembolic Disorders and Vascular Events: Discontinue MYFEMBREE if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Discontinue MYFEMBREE if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. • Bone Loss: Decreases in bone mineral density (BMD) that may not be completely reversible. Baseline and periodic BMD assessments are recommended.

	Assess risk-benefit for women with additional risk factors for bone loss. • Depression, Mood Disorders, and Suicidal Ideation: Advise patients to seek medical attention for new onset or worsening depression, anxiety, or other mood changes. • Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury. • Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop MYFEMBREE if blood pressure rises significantly. • Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing MYFEMBREE. MYFEMBREE may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue MYFEMBREE if pregnancy is confirmed. • Risk of Early Pregnancy Loss: Can cause early pregnancy loss. Advise women to use effective non-hormonal contraception. • Uterine Fibroid Prolapse or Expulsion: Advise patients to seek medical attention for severe uterine bleeding. • Hypersensitivity Reactions: Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs

Precautions	Estrogen and progestin combinations, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, especially in women at increased risk for these events. MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.
Black Box Warning	**Thromboembolic disorders and vascular events:** Estrogen and progestin combination products, including relugolix/estradiol/norethindrone, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events. Relugolix/estradiol/norethindrone is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women >35 years of age who smoke or women with uncontrolled hypertension.
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

None of the health technology Assessment agencies/institutes/authorities including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), provided a recommendation for Myfembree®.

CONCLUSION STATEMENT – MYFEMBREE®

MYFEMBREE® is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, it was approved by both FDA and EMA but not registered by SFDA yet. At the same time, none of the HTA authorities provided an assessment for the use of Myfembree® menstrual disorders. Moreover, data on a second oral GnRH antagonist, **relugolix**, combined with hormonal add-back therapy as a once daily relugolix combination therapy shows similar improvement in heavy menstrual bleeding as elagolix with add-back hormone therapy as well as similar adverse effects. **we do not recommend against adding Myfembree® for heavy menstrual bleeding once it becomes registered by SFDA.**

2.4.2 Oriahnn® (Elagolix, Estradiol, and Norethindrone Acetate)

ORIAHNN® is a combination of elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women approved by FDA in 2020. Main characteristics are listed in the table below:

Table 13. Oriahnn® Drug Information

ORIAHNN® (ELAGOLIX, ESTRADIOL, AND NORETHINDRONE ACETATE)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2020
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D25.9
Drug Class	Gonadotropin-releasing hormone (GnRH) receptor antagonist, estrogen, and a progestin combination
Drug Sub-class	-
ATC Code	-
Pharmacological Class (ASHP)	Gonadotropin-releasing hormone (GnRH) receptor antagonist, estrogen, and a progestin combination
DRUG INFORMATION	

Dosage Form	**Morning (AM) capsule: elagolix 300 mg, estradiol 1 mg, norethindrone acetate 0.5 mg.** **Evening (PM) capsule: elagolix 300 mg.**
Route of Administration	Oral use
Dose (Adult) [DDD]*	One capsule (elagolix 300 mg, estradiol 1 mg, norethindrone acetate 0.5 mg) in the morning and one capsule (elagolix 300 mg) in the evening for up to 24 months.
Maximum Daily Dose Adults*	One morning capsule and one PM capsule.
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	None
Prescribing edits*	AGE, G
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): Approved for use in adult females.	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reaction (>5%) in clinical trials were hot flushes, headache, fatigue, metrorrhagia.
Drug Interactions*	A weak to moderate inducer of cytochrome P450 (CYP3A). Co-administration with ORIAHNN may decrease plasma concentrations of drugs that are substrates of CYP3A. A weak inhibitor of CYP2C19. Co-administration with ORIAHNN may increase plasma concentrations of drugs that are substrates of CYP2C19.

	An inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ORIAHNN may increase plasma concentrations of drugs that are substrates of P-gp.
Special Population	None
Pregnancy	Exclude pregnancy before starting ORIAHNN®
Lactation	Advise the nursing female to use non-hormonal contraception until she discontinues breast-feeding.
Contraindications	High risk of arterial, venous thrombotic, or thromboembolic disorder. Pregnancy. Known osteoporosis. Current or history of breast cancer or other hormonally-sensitive malignancies. Known liver impairment or disease. Undiagnosed abnormal uterine bleeding. Known hypersensitivity to ingredients of ORIAHNN. Organic anion transporting polypeptide (OATP)1B1 inhibitors that are known or expected to significantly increase Elagolix plasma concentrations.
Monitoring Requirements	- Thromboembolic Disorders and Vascular Events: Discontinue ORIAHNN if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Stop ORIAHNN if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. - Bone Loss: Duration-dependent decreases in bone mineral density (BMD) that may not be completely

	reversible. Baseline and periodic BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss. - Suicidal Ideation and Mood Disorders: Advise patients to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes. - Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury. - Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop ORIAHNN if blood pressure rises significantly. - Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for 28 days after discontinuing ORIAHNN. ORIAHNN may delay the ability to recognize the occurrence of a pregnancy because it alters menstrual bleeding. Perform pregnancy testing if pregnancy is suspected and discontinue ORIAHNN if pregnancy is confirmed. - Risk of Allergic Reactions Due to the Inactive Ingredient (FD&C Yellow No 5): This product contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons

Precautions	Estrogen and progestin combinations, including ORIAHNN, increase the risk of thrombotic or thromboembolic disorders, especially in women at increased risk for these events. ORIAHNN is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events including women over 35 years of age who smoke or women with uncontrolled hypertension.
Black Box Warning	**Thromboembolic disorders and vascular events** Estrogen and progestin combinations increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at increased risk for these events. Elagolix, estradiol, and norethindrone is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women >35 years of age who smoke and women with uncontrolled hypertension.
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

None of the health technology Assessment agencies/institutes/authorities including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), provided a recommendation for ORIAHNN®.

CONCLUSION STATEMENT – ORIAHNN®

ORIAHNN® is a combination of Elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, it was approved by

both FDA but not registered by SFDA yet. At the same time, none of the HTA authorities provided an assessment for the use of ORIAHNN® menstrual disorders. Moreover, **Elagolix** , combined with hormonal add-back therapy was mentioned in the ACOG Practice Bulletin in 2021 for the management of symptomatic uterine leiomyomas. As a result, **we do not recommend against adding ORIAHNN® for heavy menstrual bleeding once it becomes registered by SFDA.**

Section 3.0 Key Recommendations Synthesis

Menstrual disorders are problems related to a woman's normal menstrual cycle including amenorrhea, abnormal uterine bleeding, dysmenorrhea, premenstrual syndrome (PMS), Premenstrual dysphoric disorder (PMDD) or polycystic ovarian syndrome (PCOS).

They are characterized by a variety of psycho-physical symptoms that are present in the luteal phase before menstruation and impair the quality of life of many women.

The new DSM-5 criteria for PMDD require a combination of symptoms that began in the final week before menses, started to improve in the days after onset of menses and were absent in the postmenstrual weeks during the past year.

Management options are either to reduce the effect of hormonal fluctuations linked with the menstrual cycle on neurotransmitter receptors (serotonin and GABAA). Or to inhibit the menstrual cycle by preventing ovulation.

First line treatment includes reducing effect of hormone fluctuation on neurotransmitters through lifestyle modification, Cognitive behavioral therapy (CBT)and Neuromodulators like Selective serotonin reuptake inhibitor [SSRI]/ Selective norepinephrine reuptake inhibitor [SNRI]. Combined oral contraceptive pills also reduce fluctuations in hormone level.

When irregular menstrual cycles are present, a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines.

Combined oral contraceptive pills (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.

Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric and metabolic outcomes including insulin resistance, glucose, and lipid profiles.

Two new medications were approved by FDA for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, however, both are not registered by SFDA. No changes or modifications were made to existing drugs but some drugs were withdrawn from Saudi FDA.

For MYFEMBREE®: a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, it was approved by both FDA and EMA but not registered by SFDA yet. At the same time, none of the HTA authorities provided an assessment for the use of Myfembree® menstrual disorders. Moreover, data on a second oral GnRH antagonist, **relugolix**, combined with hormonal add-back therapy as a once daily relugolix combination therapy shows similar improvement in heavy menstrual bleeding as elagolix with add-back hormone therapy as well as similar adverse effects. **we do not recommend against adding Myfembree® for heavy menstrual bleeding once it becomea registered by SFDA.**

For ORIAHNN®: a combination of Elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women, it was approved by both FDA but not registered by SFDA yet. At the same time, none of the HTA authorities provided an assessment for the use of ORIAHNN® menstrual disorders. Moreover, **Elagolix**, combined with hormonal add-back therapy was mentioned in the ACOG Practice Bulletin in 2021 for the management of symptomatic uterine leiomyomas. As a result, **we do not recommend against adding ORIAHNN® for heavy menstrual bleeding once it becomes registered by SFDA.**

Section 4.0 Conclusion

This report serves as **an annex to the previous Menstrual disorders report** and aims to provide recommendations to aid in the management of Menstrual disorders. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with menstrual disorders. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.
Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

I. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.

If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

II. What information are available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

III. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

IV. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

V. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Adopted

Grade of research[20]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. Treatment Algorithm for PMDD

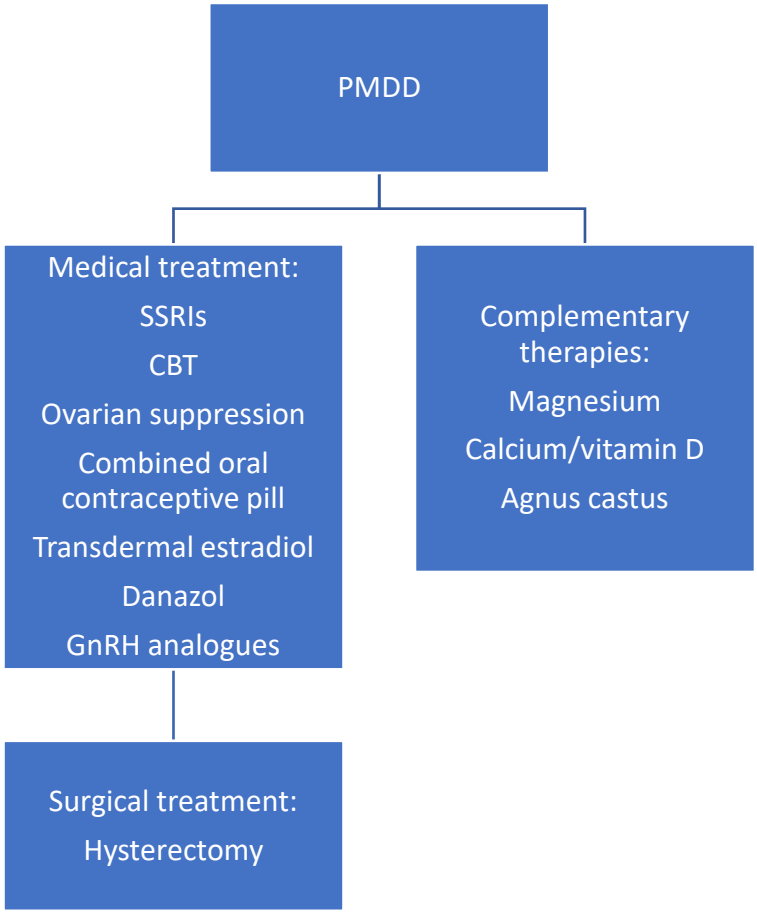

Figure 1. *PMDD Treatment Algorithm*

Appendix D. Menstrual Disorders Scope

2020 Version	Changes Performed	2023 (Current version)	Rationale/Description
Not available	New section	Scope	Summarize the main changes and updates between the 2020 and 2023 versions
Executive Summary	New section	Background	A general overview covering pathophysiological and epidemiological aspects was added.
Section 1. Menstrual disorders CLINICAL GUIDELINES			
Royal College of Obstetricians and Gynecologists: Management of Premenstrual Syndrome, November 2018	**Updated**	Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder, Royal College of Obstetricians and Gynaecologists., 2022	Takeda T. Premenstrual disorders: Premenstrual syndrome and premenstrual dysphoric disorder. J Obstet Gynaecol Res. 2023 Feb;49(2):510-518. doi: 10.1111/jog.15484. Epub 2022 Nov 1. PMID: 36317488.
International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018	**Updated**	Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome	Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, Redman LM, Boyle JA, Norman RJ, Mousa A, Joham AE. Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2023 Sep 18;108(10):2447-2469. doi: 10.1210/clinem/dgad463. PMID: 37580314; PMCID: PMC10505534.

Not available	New section	Saudi Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)	
Not available	New section	Clinical Practice Guidelines on the Diagnosis and Management of Polycystic Ovary Syndrome: A Systematic Review and Quality Assessment Study, 2021	Al Wattar BH, Fisher M, Bevington L, Talaulikar V, Davies M, Conway G, Yasmin E. Clinical Practice Guidelines on the Diagnosis and Management of Polycystic Ovary Syndrome: A Systematic Review and Quality Assessment Study. J Clin Endocrinol Metab. 2021 Jul 13;106(8):2436-2446. doi: 10.1210/clinem/dgab232. PMID: 33839790; PMCID: PMC8830055.
Not available	New section	Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, Number 228, 2021	Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, Number 228. Obstet Gynecol. 2021 Jun 1;137(6):e100-e115. doi: 10.1097/AOG.0000000000004401. PMID: 34011888.
Not available	New section	Evidence-Based Management of Premenstrual Disorders (PMDs), IAPMD Clinical Advisory Board, 2023	2023 © International Association for Premenstrual Disorders, Evidence-Based Management of Premenstrual Disorders (PMDs), IAPMD
Section 2. DRUG THERAPY FOR Menstrual disorders			
combination of elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist,	Addition of a medication	ORIAHNN® (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules	Approved by FDA in 2020 indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women

estradiol, an estrogen, and norethindrone acetate, a progestin			Not registered by SFDA No HTA recommendations
relugolix, estradiol, and norethindrone acetate	Addition of a medication	Myfembree® (relugolix, estradiol, and norethindrone acetate)	Approved by FDA in May of 2021 for the management of heavy menstrual bleeding associated with uterine fibroids premenopausal women Approved August of 2022 for the management of moderate to severe pain associated with endometriosis in premenopausal women
Not existing	**New section**	**Section 4. Key Recommendations Synthesis**	
Not existing	**New section**	**Section 5. Conclusion**	
References	Updated	**Section 6. References**	
Appendices	Updated	**Section 7. Appendices**	