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REVIEW

Emerging Perspectives on the Impact of Diabetes Mellitus and Anti-Diabetic Drugs on Premenstrual Syndrome. A Narrative Review

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ABSTRACT

Diabetes mellitus (DM) and premenstrual syndrome (PMS) are global health challenges. Both disorders are often linked to a range of physical and psychological symptoms that significantly impact the quality of life of many women. Yet, the exact relation between DM and PMS is not clear, and the management of both conditions poses a considerable challenge. In this review, we aimed to investigate the interplay between DM, anti-diabetic drugs, and the different theories and symptoms of PMS. Female sex hormones are implicated in the pathophysiology of PMS and can also impair blood glucose control. In addition, patients with diabetes face a higher susceptibility to anxiety and depression disorders, with a significant number of patients experiencing symptoms such as fatigue and difficulty concentrating, which are reported in patients with PMS as well. Complications related to diabetic medications, such as hypoglycemia (with sulfonylurea) and fluid retention (with thiazolidinediones) may also mediate PMS-like symptoms. DM can, in addition, disturb the normal gut microbiota (GM), with a consequent loss of beneficial GM metabolites that guard against PMS, particularly the short-chain fatty acids and serotonin. Among the several available anti-diabetic drugs, those (1) with an anti-inflammatory potential, (2) that can preserve the beneficial GM, and (3) possessing a lower risk for hypoglycemia, might have a favorable outcome in PMS women. Yet, well-designed clinical trials are

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needed to investigate the anti-diabetic drug(s) of choice for patients with diabetes and PMS.

Keywords: Anti-diabetic drugs; Anxiety; Depression; Diabetes mellitus; Gut microbiota; Premenstrual syndrome

Key Summary Points
Diabetes mellitus (DM) increases the incidence of premenstrual syndrome (PMS).
DM disrupts the physiological levels of estrogen, progesterone, serotonin, and gamma aminobutyric acid (GABA).
Gut dysbiosis, as a consecutive of DM, could worsen PMS severity.
Proper glycemic control may improve the PMS symptoms.
Clinical studies are required to investigate the anti-diabetic drug of choice for PMS-diabetic women.

INTRODUCTION

Premenstrual syndrome (PMS) is one form of the premenstrual disorders which consist of a wide range of psycho-somatic symptoms occurring in the luteal phase of the menstrual cycle. Once the symptoms become severe to the point of debilitation, it meets the criteria of premenstrual dysphoric disorder (PMDD). Approximately 20–40% of young women suffer from PMS, 2–8% from PMDD, and 85% suffer from at least one symptom of PMS during their child-bearing years [1, 2].

According to the International Diabetes Federation (IDF) 2021, at least 537 million adults are now living with diabetes mellitus (DM) and this number is increasing dramatically every year [3]. PMS and DM share many physical and psychological symptoms [4]. Thus, diabetic women with PMS might be more prone to severe physical and psychological manifestations that require specific care and attention. This review aims to discuss the contemporary theories of PMS, the relation between DM and PMS, and the possible impact of the different anti-diabetic drugs on PMS sequelae. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

FEMALE SEX HORMONES AND MENSTRUAL CYCLE

Estrogen and progesterone are the two main female sex hormones that control the menstrual cycle under the regulation of the gonadotropin-releasing hormone (GnRH) and with the orchestration of: the follicular stimulating hormone (FSH) and the luteinizing hormone (LH). Although the plasma levels of these hormones change all through the menstrual cycle, these changes at each particular phase are responsible for parallel physiological actions [5], as detailed in Fig. 1.

Estrogen synthesis is dependent on the action of the aromatase enzyme, which is a cytochrome p450 (CYP450) enzyme. This enzyme converts androstenedione to Estrone (E1), the precursor of the other available estrogen forms: Estradiol (E2), estriol (during pregnancy), and estetrol (in fetal liver). Estrogen exerts its action by binding to estrogen receptor (ER)α, ERβ, and G-protein coupled receptors (GPCR) and is extensively metabolized by the CYP450 system [6]. Progesterone is synthesized from cholesterol through the precursor pregnanolone sulfate to act on nuclear and extra-nuclear membrane associated kinases. Progesterone is metabolized into: allopregnanolone, estrone, estradiol, and testosterone, all of which are substrates for and/or modifiers of CYP450-dependent metabolism [7]. Both estrogen and progesterone are lipophilic hormones that can pass readily to the brain and can be localized in cortical and subcortical regions. In the central nervous system, these hormones are involved in the reproductive and neuroendocrine functions.

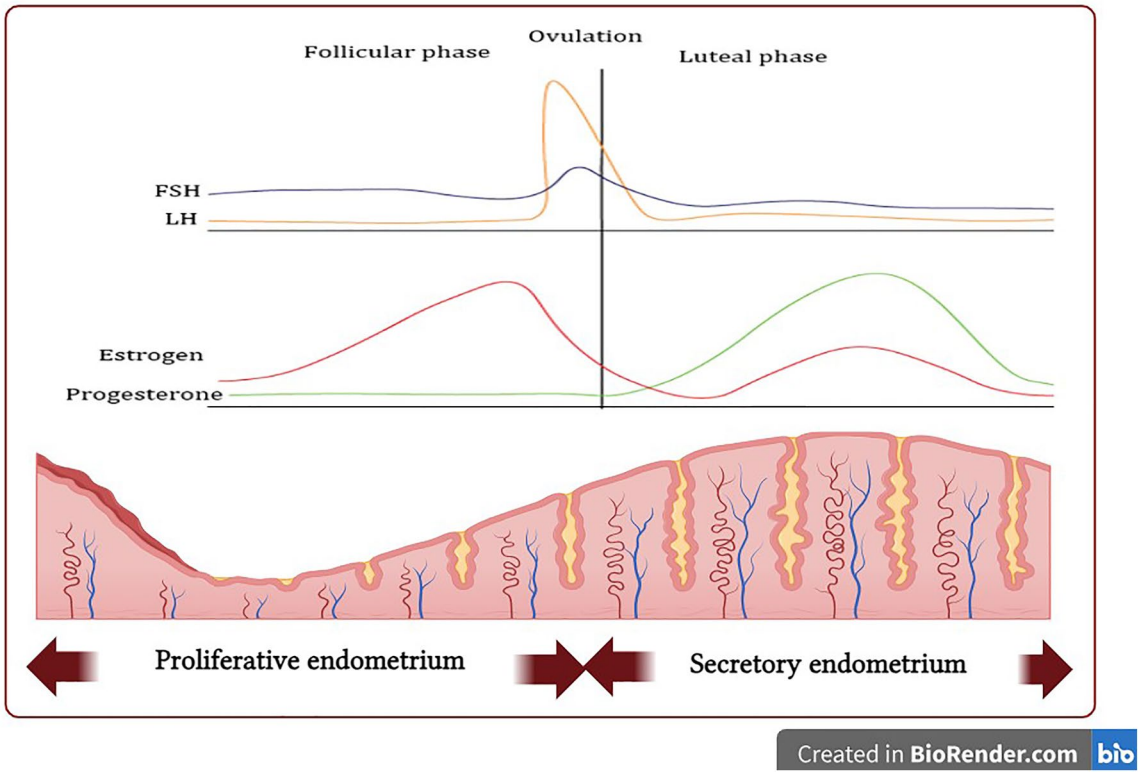

Fig. 1 The follicular phase (lasting for ~ 14 days in an average 28-day cycle) starts with the secretory function of the hypothalamus, which secretes the gonadotropin-releasing hormone (GnRH) that stimulates the anterior pituitary to secrete the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). LH stimulates the theca cells in the ovarian follicles to produce progesterone and androstenedione through the activation of the cholesterol desmolase enzyme. Androstenedione then diffuses to the granulosa cells in the ovarian follicle where it is converted under the effect of the FSH into estrone (E1) (by the action of the aromatase enzyme) and testosterone (by the action of 17β-hydroxysteroid dehydrogenases). Subsequently, by the action of the aromatase enzyme testosterone is converted into estradiol (E2) and by the action of the 17β-hydroxysteroid dehydrogenases, E1 is converted to E2. As the levels of estrogen and progesterone are increased, negative feedback from both hormones decreases the FSH and LH secretion. At the time of ovulation, and at a certain threshold of the estradiol that was continuously produced by the maturating ovarian follicles, positive feedback to the anterior pituitary occurs, resulting in LH surge and hence the ovulation occurs. In the luteal phase (lasting for ~ 14 days in an average 28-day cycle), progesterone under the effect of LH dominates to prepare the endometrium for fertilization. At the end of the luteal phase and in absence of conception, progesterone negatively decreases FSH and LH secretion with subsequent decrease in E2 and progesterone production. This results in endometrium shedding and menstruation begins

They are also involved in the memory and the emotional processes [8]. Allopregnanolone and estradiol are considered neurosteroids that can be synthesized de novo in the brain with evidence supporting the persistence of allopregnanolone in plasma even after surgical or pharmacological adrenalectomy or gonadectomy [9].

FEMALE SEX HORMONES AND PMS THEORIES

Premenstrual disorders (PMDs) refer to premenstrual syndrome (PMS) and the severe disabling form, the premenstrual dysphoric disorder (PMDD). Both disorders manifest with physical and psychological symptoms that may include

one or more of the following: headache, fatigue, sleep disorders, edema, fluid retention, weight gain, abdominal bloating, lack of concentration, irritability, food craving/change in appetite, anxiety, and depression. According to the Royal College of Obstetricians and Gynecologists, diagnosis of PMS necessitates occurrence of any of these symptoms during the luteal phase of at least two-successive menstrual cycles. On the other hand, PMDD is diagnosed with at least one psychological symptom, together with at least five of the other symptoms in two or more consecutive cycles [10].

Numerous studies are aimed at identifying the underlying pathophysiology of PMS, yet these studies have only generated a few theories, which require further verification for a comprehensive understanding of the condition. In several studies, estrogen and progesterone levels did not show significant variation between women with and without PMS [11]. However, Redei et al. [12] found that severe PMS symptoms are positively correlated with estradiol and progesterone levels at the early luteal phase. Hence, it is now accepted that fluctuation and altered sensitivity rather than the absolute levels of estrogen and progesterone are correlated to PMS prevalence and severity [13]. In susceptible women, estrogen, progesterone, allopregnanolone, and pregnanolone sulfate can influence aldosterone actions and increase nitric oxide levels, thus mediating edema/breast tenderness and headache, respectively [14–16]. Allopregnanolone also has a central gamma aminobutyric acid type A receptor ($GABA_A$) modulating action. In the early luteal phase, exposure to high levels of allopregnanolones may desensitize $GABA_A$ receptors and result in anxiety [17, 18]. Estrogen and progesterone fluctuations may cause significant changes in serotonin's levels and actions. This abnormal serotonin will predispose to the dramatic mood swings reported by patients with PMS such as: irritability, anxiety, depression, besides the lack of concentration and the changes in appetite [10, 19] as detailed in Table 1.

An inflammation theory of PMS has also recently gained its acceptance from several clinical studies that reported high levels of inflammatory and oxidative stress markers in patients with PMS [30]. Tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β), IL-6, and IL10 were all found to be elevated in, and associated with severe PMS symptoms [31]. Highly sensitive C-reactive protein (hs-CRP) levels < 3 mg/l was also found to be correlated with mood disorders, food craving, weight gain, breast tenderness, abdominal pain, and bony aches experienced during the PMS period [32, 33]. Inflammation may result in (1) hypothalamic–pituitary–adrenal axis dysfunction (revealed as dysregulated sex hormones, cortisol, and catecholamines levels), (2) abnormal serotonin metabolism, and (3) a malfunctioning GABAergic system [34], all of which could end in PMS. Although estrogen and progesterone have anti-inflammatory and antioxidant actions, their abnormally high levels and the products of the estrogen metabolism might result in pro-oxidative actions through releasing reactive oxygen species (ROS), manifesting as PMS [35].

FEMALE SEX HORMONES AND DM

It is a well-known fact that the hyperglycemia associated with type 1 DM (T1DM) and type 2 DM (T2DM) is due to an absolute or a relative insulin deficiency, respectively. Insulin resistance (IR), which refers to abnormally decreased insulin actions, is almost always observed in patients with T2DM. Recent studies, however, point to the possible association of IR with T1DM as well. This state of IR results in loss of the favorable metabolic and anabolic actions of insulin. In T2DM patients with a relatively preserved pancreatic β cells function, hyperinsulinemia occurs and causes further β cells exhaustion, with a progressive deterioration in the patient's glucose homeostasis [36]. Hyperglycemia, hyperinsulinemia, and IR are implicated in the diverse macrovascular and microvascular complications of DM through increasing the level of the advanced glycation end products and the formation of mitochondrial ROS. This causes activation of proinflammatory and polyol pathways, increased plasminogen activator inhibitor-1 production, inactivation of important anti-atherosclerotic

Table 1 Comparison between estrogen and progesterone as regards their impact on premenstrual syndrome pathophysiology

	Estrogen	Progesterone
Serotonin [20, 21]	Estrogen increases the degradation of the mono-amino oxidase (MAO)-A enzyme that is responsible for serotonin breakdown, thus increasing serotonin levels Estrogen can also enhance the expression of the serotonin transporters (SERT) and serotonin receptors Excess estrogen can decrease serotonin production	Progesterone enhances MAO-A activity, decreasing serotonin levels
Gamma aminobutyric acid (GABA) [21, 22]	Estrogen can enhance brain-derived neurotrophic factor (BDNF) that promotes GABA transmission and activity. However, high estradiol levels were found to reduce cortical GABA levels	The progesterone metabolite allopregnanolone is a gamma aminobutyric acid type-A receptor ($GABA_A$) positive modulator with anxiolytic action, but could bring out fatigue The progesterone precursor pregnanolone sulfate instead has an anxiogenic action
Fluid retention [23]	Excess estrogen increases aldosterone that could cause fluid retention and manifest with edema	Progesterone has mineralocorticoid-like action and can stimulate aldosterone secretion, resulting in fluid retention and edema
Nitric oxide (NO) [24, 25]	Increased estrogen level, increases NO production, resulting in edema and headache	Increased progesterone increases NO production, resulting in edema and headache
Appetite [26]	Decreases appetite	Increases appetite
Cortisol [27, 28]	Estrogen administration (estradiol 2 mg/day) was found to increase cortisol levels	Progesterone and allopregnanolone can be converted into cortisol during stress periods
Norepinephrine (NE) [29]	Low estrogen can increase NE release, where the latter decreases serotonin, dopamine, and acetylcholine: resulting in fatigue, depression, insomnia, and appetite changes	Progesterone can prevent NE depletion

enzymes (nitric oxide synthase and prostacyclin synthase), raising the level of the atherogenic cholesterol-rich apo B-containing lipoproteins. These hazardous actions could be manifested by microvascular pathologies (retinopathy, nephropathy, and neuropathy) and macrovascular pathologies (myocardial ischemia and cerebrovascular stroke) [37, 38].

The relation between female sex hormones and DM starts as early as puberty. In fact, some studies correlated having an earlier menarche age (less than 9 years old) or a late menarche (after the age of 17) with a higher risk for

T2DM [39, 40]. In addition, perimenopausal women with T2DM show more irregularity of menstrual cycle length with lower fertility potential than do their aged-matched non-diabetic women [41]. Although the explanation of such an association is not known with certainty, it might be explained on the grounds of increased tendency towards sedentary life and obesity in this age group. This lifestyle may cause low insulin sensitivity and hyperinsulinemia, both of which can disturb the normal gonadotropin-ovarian function and increase the risk of polycystic ovarian syndrome (PCO) [42].

Insulin has direct and indirect actions on the female reproductive system. The direct actions are evident by the expression of insulin and insulin growth factor-1 (IGF-1) receptors on the ovaries, upon which insulin can bind and exert its influence on steroidogenesis [43]. Under physiological conditions, insulin acts to facilitate the GnRH actions on: (1) LH (to increase androgen production and induce luteinization of granulosa cells to produce progesterone), and on (2) FSH (to increase estrogen production) [44]. In PCO patients, excess insulin increases the production of androstenedione and progesterone and was found to reduce E2 concentration [45, 46]. Subsequently, excess androgen can result in more IR [47] that together with the abnormally high LH surge would result in arresting the follicular growth, leading to anovulatory cycles [48].

Not only may DM affect the normal physiology of the menstrual cycle, but estrogen and progesterone have also shown significant impacts on blood glucose levels. The action of estrogen on blood glucose is complex and seems to be dependent on the pre-existing estrogen level. In postmenopausal diabetic women, estrogen replacement therapy was reported to improve glycemic control. Paradoxically, hyperestrogenism was reported to cause a state of IR that could share in the development of gestational diabetes and PCO [49]. To better understand these contradictory actions of estrogen on blood glucose, we should notice that the physiological concentrations of E2, through acting on ERα, can increase the expression of the insulin gene and the pancreatic insulin content, and hence improve insulin sensitivity without affecting the pancreatic β cells mass [50]. ERα also plays an important role in the expression of the glucose transporter 4 (GLUT4) in skeletal muscles and so can aid in glucose uptake. In contrast, excess estrogen was found to downregulate E2-dependent liver X receptors (LXRs) which could decrease the expression of GLUT4 and activate the gluconeogenic process, mediating IR and hyperglycemia [51]. Also, abnormally low E2 levels and distorted ERα action were found to induce hypertrophy in the white adipose tissue that could induce and/or aggravate IR ending up with T2DM [52]. In addition, in female mice, abnormal ERα function in the hypothalamus was reported to cause hyperphagia, hyperglycemia and weight gain [53]. Progesterone can also disturb glucose homeostasis, which is evident by its role in the development of gestational diabetes through its actions on the progesterone receptor membrane component 1(PGRMC1) in the liver that promotes gluconeogenesis and worsens glycemic control [54].

DM AND PMS

As mentioned previously, DM and PMS share many physical and psychological symptoms. The diverse group of somatic PMS symptoms such as fatigue, headache, and lack of concentration can be observed in patients with diabetes and refers to the loss of the metabolic actions of insulin and the poor glycemic control [55]. Diabetic nephropathy, as well as some anti-diabetic drugs (e.g., thiazolidinedione), may also cause fluid retention and worsen PMS-related edema [56]. Compared to non-diabetic patients, patients with diabetes have a higher incidence of anxiety and depression disorders compared to non-diabetic patients [57, 58]. Both anxiety and depression represent the most common psychological disorders reported in patients with PMS. In patients with diabetes, low levels of brain-derived neurotrophic factor (BDNF) and the depletion of the brain serotonin were reported and encountered in the development and progression of anxiety and depression [59, 60]. Furthermore, patients with diabetes have

increased levels of inflammatory cytokines (e.g., IL-6 and TNFα) that can mediate what is called "cortisol neurotoxicity" in the hippocampus. This disorder is manifested by mood and cognitive disorders that can predispose to PMS-like symptoms as well [61]. In addition, Smith et al. [62] referred to symptoms-related worries and illness-progression phobias as an explanation to mood disorders reported in patients with diabetes. Thus, the co-existence of DM and PMS are hypothesized to worsen the patients' complaints as regards the prevalence, the severity of symptoms, and the response to treatment.

Do DM and PMS Affect Each Other?

Although the impact of DM on PMS has been investigated in several studies, the results of those studies are not enough to understand their possible relation. Few studies have considered the possible association between DM and PMS [63–65]. Some studies tackled the impact of the different menstrual cycle phases on blood glucose and IR [63, 64, 66–72], while some studies investigated the impact of blood glucose changes on PMS symptoms, but in non-diabetic women [73, 74]. In terms of prevalence, Huang et al. [65] noted an association between DM and PMS. In contrast, Machfudhoh et al. [75] concluded that children with T1DM have no or only mild PMS. Similarly, Cawood et al. [63] also noticed that PMS symptoms in diabetic women are fewer than they are in non-diabetic women. Regarding severity, patients with diabetes with proper glycemic control did not appear to have milder PMS symptoms [63]. This finding defended the implication of DM in the development of PMS. Contrary, Creţu et al. [42] and Huang et al. [65] described diabetic women with insulin-related hyper-progesterone as being at higher risk for PMS. Regarding the impact of blood glucose level on PMS symptoms, Zarei et al. [74] concluded that hypoglycemia is a stimulating factor of PMS, which is in contrast to Cawood et al. [63] and [76], who reported some PMS symptoms (like anxiety and food craving) to be correlated to hyperglycemia and not to hypoglycemia.

On the other hand, as for the influence of the different menstrual cycle phases on blood glucose and insulin levels, Spellacy et al. [66] found no significant changes in plasma glucose or insulin levels in either the follicular or the luteal phases in both PMS and healthy-matched women. On the contrary, Trout et al. [72] reported high fasting glucose and low insulin sensitivity during the luteal phase, yet this finding was not significant. Dey et al. [64] similarly reported increased blood glucose level in the same phase. Also, Denicoff et al. [73] reported significant changes in glucose tolerance test in both luteal and follicular phases, but they denied PMS to be related to these changes.

These contradictory findings can be explained in the view of the methods used to evaluate the PMS–DM relationship. Although the diagnosis of PMS is an easy questionnaire-based process, the method and timing of blood glucose and insulin measurement made the interpretation of those studies challenging. Many studies relied on measuring fasting blood glucose and fasting insulin levels and estimating IR using the homeostatic model for assessment of IR (HOMA-IR). However, continuous blood glucose and insulin monitoring should have been ensured by using hyperinsulinemic-euglycemic clamp to avoid any subjective appraisal that might mislead the analysis of the blood glucose records. The exact timing between the change in blood glucose and the occurrence of mood alteration or the appearance of PMS physical symptoms has not been yet defined. In addition, the glycemic threshold for mood alteration has not been determined. Besides, individual variations and preexisting psychological and hormonal disorders could all affect the presentation of PMS in patients with diabetes.

To better understand the possible role of DM in PMS, it is important to notice that the important anabolic actions of insulin can help improve fatigue and the lack of concentration expressed by many patients. Insulin receptors additionally are widely distributed in the body, including the nervous system. In the brain, insulin receptors not only facilitate glucose delivery to this vital organ but they also improve synaptic plasticity and stimulate the release of neurotrophic factors (e.g., BDNF), hence exerting an anti-depressant

action [77]. This finding was supported by many experimental studies and clinical trials in which insulin succeeded to improve depression symptoms through different mechanisms, including interacting with *N*-methyl-D-aspartic acid (NMDA) receptors in the hippocampus and by regulating neuronal cell growth and survival [78, 79]. Insulin also plays a vital role in the regulation of the autophagy process, as it facilitates the clearance of the damaged and aging organelles. Any defect of this cleansing process is associated with an increased ROS formation besides a subsequent neuronal cell death [80]. Insulin, in addition, has a major impact on brain serotonin by increasing the delivery of tryptophan to the brain, increasing the activity of the tryptophan hydroxylase enzyme, and decreasing the activity of the MAO enzymes, all of which enhance neuronal serotonin synthesis and concentration [81]. Thus, insulin deficiency and IR can be contributing factors for some PMS symptoms such as food craving, fatigue, lack of concentration, depression, and anxiety.

It seems that both hypoglycemia and hyperglycemia are linked to PMS, even though the fluctuation in blood glucose is not limited to the luteal phase. It is important to note that hypoglycemia is almost always represented as an acute episode because long-standing hypoglycemia can lead to irreversible brain damage. Through stimulating sympathetic nervous system and catecholamines secretion, hypoglycemia can be manifested with lack of concentration, anxiety, palpitation, nervousness, and irritability that mimic PMS symptoms [65, 72]. However, Denicoff et al. [73] concluded that despite the similarities between the symptoms of PMS and hypoglycemia, these two conditions can be effectively distinguished based on their respective spectrum of symptoms. On the other hand, hyperglycemia can be acute postprandial or chronic poorly controlled hyperglycemia. Acute hyperglycemia can cause a significant distortion of cognitive functions, e.g., information processing, attention, and working memory (letter/number sequencing) in addition to decreased alertness and happiness [42]. While chronic hyperglycemia may cause higher progesterone levels and neuropathy leading to PMS-related symptoms, this long-standing condition also allows for better cerebral adaptation.

Can Gut Microbiota Link DM and PMS?

Gut microbiota (GM) has recently gained researchers' interest due to their major impact on body systems. GM play a pivotal role in the synthesis of many neurotransmitters (e.g., dopamine, serotonin, GABA, norepinephrine, and choline) and short-chain fatty acids (SCFA) (e.g., butyrate and succinate) that influence our body's well-being. Gut dysbiosis (which refers to the systemic translocation of GM) has been speculated to mediate many psychological and somatic symptoms of PMS through inducing a state of systemic inflammation and neurodegeneration and causing abnormal hormonal levels [82]. Exposure of the systemic immune cells to the bacterial lipopolysaccharide (LPS) was found to increase the risk of T2DM [83] and was correlated to PMS as well [31]. Furthermore, marked differences in the GM composition were reported between diabetic and non-diabetic patients [84, 85].

The SCFAs synthesized by our GM have anti-inflammatory actions, being able to suppress IL-6, NO, and TNFα production and prevent the systemic translocation of the bacterial LPS [86]. SCFA was also found to be correlated with a lower risk of developing T1DM [87]. These SCFA also play a protective role in many neuropsychiatric disorders such as anxiety, depression, and neurodegeneration [88]. Bourassa et al. [89] mentioned in their study that the anti-oxidative action of butyrate can enhance the transcription of some protective proteins that are able to guard against neurodegeneration. In support of the possible GM role in PMS, Takeda et al. [90] described in their study a positive association between low levels of *Butyricicoccus*, *Megasphaera*, and *Parabacteroides* (known for their butyrate secretion action) and the prevalence of PMDs. The secretory function of GM, which includes serotonin, dopamine, and norepinephrine, shares at least in a part in the positive impact of probiotics on the aforementioned disorders. Moreover, *Lactobacillus* and *Bifidobacterium* were found to be able to metabolize

glutamate to produce GABA [91] and can also improve the BDNF level [92].

Regarding female steroid hormones, GM can enhance estrogen concentration through secreting β-glucuronidase enzymes. These enzymes deconjugate the estrogen secreted in bile into active functioning forms. Sovijit and colleagues [93] also demonstrated a positive relation between *Lactobacillus* and progesterone levels.

ROLE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PMS MANAGEMENT

The Food and Drug Administration (FDA) has approved the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, and paroxetine as first-line treatment for PMS [94]. Unlike the delayed response of the SSRIs in the treatment of depression, the rapid response to SSRIs in patients with PMS was explained by another mechanism rather than increasing serotonin levels at the post-synaptic serotonergic nerves. SSRIs were found to facilitate GABAminergic transmission by affecting progesterone metabolism and by increasing levels of allopregnanolone. SSRIs can also improve insulin sensitivity and improve glucose homeostasis [95, 96]. These actions allowed prescribing these medications to control some of the PMS symptoms. Yet, it should be noticed that SSRIs can impair blood glucose control, predisposing to hypoglycemia when prescribed with some anti-diabetic medications, particularly the glitazones, as discussed later in "Glitazones" section.

ANTI-DIABETIC DRUGS AND PMS

In contrast to DM, which has international guidelines for management, the concomitant presence of PMS with DM has no specific rules to follow. Among the available different anti-diabetic drugs, patients with diabetes and PMS should be advised with drug(s) with the least probability to worsen their PMS condition, or drugs that would rather improve their PMS-related complaints. Due to the paucity of clinical studies that studied the impact of the anti-diabetic drugs on PMS, we will discuss the possible role of these drugs on PMS based on their cross-talk with the PMS theories. In general, anti-diabetic drugs that would provide better control for the primary diabetic disease are speculated to eliminate any further burden of this metabolic disorder on PMS etiologies and presentations. Achieving a nearly constant blood glucose level can minimize aggravation of PMS symptoms. Adopting the inflammatory theory on PMS would give an expectation for anti-diabetic drugs with an anti-inflammatory potential to improve PMS symptoms. Also, drugs that can preserve an ecosystem of healthy and functioning microbiota can directly protect against and improve PMS in susceptible women.

Insulin and Insulin Secretagogues

Ever since their first introduction to the market, insulin and the insulin secretagogue sulfonylureas (SU) have been continuously developed to improve their pharmacokinetic and pharmacodynamic properties. Meglitinides have a similar action as that of SUs, but they act on different receptors with weaker binding affinity and faster dissociation [97, 98]. By preserving the anabolic and neuroprotective actions of insulin, insulin secretagogues are expected to improve some of the related PMS symptoms. Yet, increased insulin levels in the presence of insulin resistance may carry a higher risk of PMS through the hazardous actions of hyperinsulinemia, e.g., PCO [48].

SUs have the highest risk of hypoglycemia among the different anti-diabetic drugs. As mentioned before, hypoglycemia associated with catecholamine surge is manifested by PMS-like symptoms [65, 96]. Moreover, chlorpropamide, one of the old-generation SUs has the tendency to cause fluid retention due to an anti-diuretic hormone (ADH)-mediated action [99]. This action could aggravate the fluid retention and mastalgia experienced during PMS. It is to be noted also that chlorpropamide has been reported to increase serotonin levels by decreasing the latter's metabolism [100]. Tolbutamide,

another old-generation SU, has shown a positive impact on the activity of the serotonergic neurons [101]. Along with the cross-talk between SUs and serotonin, SU can also increase GABA activity through the inactivation of the ATP-sensitive K^+ channels in the substantia nigra, improving the PMS-related anxiety symptoms and improving the pattern of sleep [102]. Both SUs and meglitinides possess anti-inflammatory actions that may contribute to improving PMS pathogenesis. Meglitinides were found to decrease oxidative stress and inflammatory markers such as IL-6, IL-18, and also TNFα. Similarly, the newer-generation SU glibenclamide was found to be able to inhibit the nuclear factor kappa B (NF-κB)-mediated inflammatory pathways and to decrease the secretion of some inflammatory cytokines (TNF-α, IL-1β, ROS). Through inhibiting the depolarization of the sulfonylurea type 1-transient receptor potential melastatin 4 (Sur1-Trpm4) channels, glibenclamide can also protect against neuronal cell death [103, 104].

Metformin

Metformin was the first known insulin-sensitizing agent pursued by the French physician Jean Sterne in 1957. The insulin-sensitizing action of metformin is executed by increasing peripheral glucose uptake and utilization that ensures euglycemic level. Other anti-diabetic actions of metformin include reducing hepatic gluconeogenesis, decreasing intestinal glucose absorption, and stimulating satiety [104, 105].

The new insights into the role of metformin in upstreaming the AMP-activated protein kinase (AMPK) have provided a unified explanation for the beneficial actions of metformin, not only as an anti-diabetic drug, but also in other metabolic, endocrinal, and neuropsychiatric disorders [104]. AMPK activation has been linked to many cellular processes, for example glucose and lipid metabolism, autophagy, and apoptosis, in addition to mediating an anti-oxidant effect. AMPK is also one of the downstream regulators of the tumor suppressors such as p53 [106].

Estradiol action on ERα was found to repress the AMPK activity and hence increase the risk for estrogen-dependent breast and endometrial cancers [107]. Metformin in turn has the potential to inhibit the expression of the aromatase enzyme, decreasing estrogen production. Metformin can also inhibit the nuclear translocation of cyclic AMP-responsive element binding protein-regulated transcription coactivator 2 (CRTC2), a coactivator of aromatase expression, and subsequently decreases estrogen concentration [108]. As far as its effect on sex hormones regulation, metformin has a unique place among all the anti-diabetic drugs in patients with PMS with abnormal high estrogen levels or estrogen sensitivity. Furthermore, in PCO patients with relatively low estrogen, metformin can treat hyperandrogenism, improve plasma estrogen levels, normalize menstrual irregularities, increase progesterone receptor expression, and improve progesterone concentration [109–113]. These actions suggest a possible impact for metformin in PMS according to the baseline estrogen level. The anti-inflammatory actions of metformin could also aid in improving PMS symptoms. At the cellular level, the anti-inflammatory effects of metformin include reducing the expression of NF-κB, decreasing NF-κB-mediated inflammatory signals, and inhibiting the differentiation of monocyte into macrophages. It also reduces the production of TNF-α, IL-6, and IL-8 from epithelial cells and macrophages. These findings are supported by a meta-analysis that included 216 clinical trials carried out on PCO patients where metformin significantly reduced CRP levels [114]. The antioxidant role of metformin is carried out through several mechanisms: (1) direct trapping of hydroxyl radicals, (2) activation of antioxidant enzymes such as catalase, which is the main decomposer of H_2O_2, and (3) reducing the transcription and activation of NADPH oxidase 4 (NOX4), which is a major source of oxidative stress [115].

At the level of the nervous system, metformin has shown a favorable impact on anxiety and depression secondary to diabetes by influencing GABA and serotonin actions. Metformin exerts its action on the GABAergic system by directly regulating the number of neurotransmitters released and improving the expression of the receptors on the postsynaptic membrane

[116]. Fan et al. [117] demonstrated that metformin potentiates inhibitory synaptic transmission by enhancing the postsynaptic accumulation of $GABA_A$ receptors in the cell membrane by activating the AMPK- Forkhead transcriptional factor (FoxO3a) signaling pathway and increasing the expression of $GABA_A$ receptor-associated protein. Moreover, the antidepressant effect of metformin observed in diabetic and PCO patients could be attributed to the elevation of serotonin and norepinephrine levels in the brain and the modulatory action of metformin on the hypothalamic serotonin axis [118, 119]. Metformin can also stimulate the release of serotonin from the enterochromaffin cells via neuronal and non-neuronal mechanisms. Yet, metformin may inhibit the uptake of serotonin from the intestinal lumen, leading to the accumulation of serotonin in the gut [120]. It remains uncertain whether this action would have a positive impact on the brain's serotonin levels.

Glitazones

Thiazolidinediones (TZDs), also called glitazones, elicit their insulin-sensitizing action either through a direct pathway (the fatty acid steal hypothesis) or indirectly (via modulating the adipokines release and upregulating the adiponectin production genes) by way of being selective agonists to the transcription factor, nuclear peroxisome proliferator-activated receptors (PPARs). Although PPARs exist in three isoforms, PPAR-α, PPAR-β, and PPAR-γ, TZDs possess a stronger binding affinity to PPAR-γ subtype [121].

Genetic studies have linked genetic polymorphism of PPAR-γ to PCO pathology, suggesting a link between PPAR-γ and the hypothalamic–pituitary–gonadal axis. Clinical studies in addition have reported an effect for TZDs therapy on improving hyperandrogenism and decreasing high LH levels in PCO patients [122]. Furthermore, adiponectin receptors (AdipoR1 and AdipoR2) were found to be regulated by PPAR-γ. These adiponectin receptors are widely expressed along the hypothalamic–pituitary–ovarian axis where they exert an inhibitory effect on the secretion of GnRH from hypothalamic cells. In the gonadotropic cells of the pituitary gland, adiponectins can stimulate LH and FSH synthesis and secretion. Finally, at the ovarian level, adiporeceptors expressed in the human granulosa cells regulate steroidogenesis, increasing progesterone and estradiol secretion in the presence of FSH and IGF-1 [123, 124]. In vitro studies illustrated the ability of TZDs to inhibit progesterone and estradiol secretion by human granulosa cells obtained from young women after hCG stimulation for in vitro fertilization, or from PCO patients. This can be attributed to the negative effects of TZDs on the activity of the steroidogenic enzymes: 3-beta-hydroxysteroid-dehydrogenase (3-βHSD) and the aromatase enzyme [125, 126]. Notably, Froment et al. [126] stated that treatment by TZDs does not seem to affect the secretion levels of prolactin, FSH, or LH.

The engagement of TDZs in regulating the above-mentioned hormones is hypothesized to impact PMS outcome, especially that TZDs may have a neuroprotective and an anti-inflammatory potential in the central nervous system. These actions are mediated by the TZDs' inhibitory activity on the ability of macrophages to produce TNFα, IL-6, inducible nitric oxide synthase, COX-2, and IL-1β, through the down-regulation of their genes. This is along with the TZDs' positive action on adiponectin genes, which are known to possess a potent anti-inflammatory action as well [127, 128]. Being able to ameliorate the chronic inflammatory status seen in insulin resistant, TZDs may help to attenuate the PMS inflammatory etiology.

TZDs, in some clinical studies, have demonstrated a positive potential in the treatment of major depression, especially when associated with insulin resistance. This finding was supported by a double-blinded randomized controlled trial (RCT) that assessed the effect of pioglitazone as an adjuvant treatment on depressive symptoms. The authors stated that there was a significant improvement in depression symptoms, but only in patients with insulin resistance, as a consequence of a better glucose homeostasis [129]. Another RCT by Sepanjnia et al. reported pioglitazone as a beneficial and safe short-term adjunctive modality

in non-diabetic patients with depression as it showed higher rates of early improvement [130].

It was reported that TZDs are associated with dose-related fluid retention in about 20% of treated patients. In most patients, the edema is mild and responds to diuretics [131]. However, in diabetic women with PMS symptoms, TZDs may increase the burden of edema and breast tenderness. TZDs are not known to cause hypoglycemia when used as monotherapy. However, hypoglycemia may develop when being administered with other oral hypoglycemic drugs (particularly sulfonylurea), or when concomitantly prescribed with serotonin selective reuptake inhibitors (SSRIs) [132, 133]. The interaction with the later drug is particularly of great concern as SSRIs are commonly prescribed for PMS management. TZDs have other drug–drug interactions of special interest in patients with PMS, particularly the concomitant administration of pioglitazone with oral contraceptives containing ethinyl estradiol or norethindrone, which are prescribed in some cases either for birth control or to improve PMS symptoms. This combination may lead to a decrease in the plasma concentrations of the contraceptive hormones and consequently to the loss of their contraceptive effect [134].

In brief, the use of TZDs in patients with diabetes and PMS carries many concerns, despite the potent role of TZDs in improving insulin resistance and their anti-inflammatory potential that are expected to improve the diabetic-related PMS pathologies. Yet, TZDs increase the incidence of fluid retention, interact with sex hormones, and most importantly their concomitant use with SSRI carries higher risk for hypoglycemia.

Incretins: Glucagon-Like Peptide-1 Agonists and Dipeptidyl Peptidase 4 Inhibitors

Incretins are a group of gut peptides that stimulate insulin secretion and glucose homeostasis after nutrient intake. Glucagon-like peptide 1 (GLP-1) is one of those incretins. It is secreted from the intestinal epithelial L-cells to act on GLP-1 receptors (GLP-1Rs) which mediate its metabolic and extra-metabolic actions [135]. GLP-1 protects against hyperglycemia by enhancing insulin secretion through the regulation of the ATP-sensitive K^+ channels in the pancreas. They can also inhibit glucagon secretion through the activation of the GLP-1 receptors present in the pancreatic α-cells by a protein kinase A (PKA) -dependent inhibition of P/Q-type Ca^{2+} channels in the pancreas. This action suppresses glucagon exocytosis [136, 137]. Based on these actions, GLP-1 R agonists (GLP-1RAs), e.g., liraglutide, exenatide, and semaglutide, are now approved as first-line agents for the management of T2DM [138].

GLP-1RAs have some neuro-endocrinal-metabolic actions that might link them to PMS. Although experimental studies have demonstrated that the acute activation of GLP-1R could increase serotonin turnover, chronic GLP-1RA administration has shown improvement in the serotonin receptor expression in the amygdala where it succeeded to implement an anti-depression action [139]. GLP-1RAs, in addition, stimulate the activity of the carbonic acid decarboxylase enzyme, increasing the decarboxylation of glutamate into GABA, and hence elevating brain GABA levels [140]. As regards the endocrinal effects, despite the shortage of information on the clinical effects of GLP-1/GLP-1RAs on the hypothalamic–pituitary–ovarian hormones, experimental studies have demonstrated a potent effect of GLP-1RAs on regulating the hypothalamic–pituitary–adrenal axis. GLP-1RAs can suppress aldosterone production, which may improve fluid retention in the premenstrual phase [141]. In rats, GLP-1RAs also exhibited a positive impact on estradiol and progesterone levels along the estrous cycle [142]. In humans, a close relation between progesterone and GLP-1 has been recognized, as enteral progesterone was found to increase plasma levels of GLP-1. In addition, progesterone receptor membrane component 1 (PGRMC1) expressed on pancreatic β cells was found to interact with the activated GLP-1R to enhance the insulinotropic actions of GLP-1 [143].

GLP-1RAs exert an anti-inflammatory effect on vascular endothelial cells by upregulating the activity and the expression of the endothelial nitric oxide synthase (eNOS) and by inactivating the NF-κB signaling pathway [144]. Unlike

other antidiabetic drugs, GLP-1RAs do not cause hypoglycemia, even in combination regimens. So these drugs are not expected to cause PMS-like symptoms that are related to hypoglycemia. GLP-1RAs can also suppress food intake by acting on different areas in the hypothalamus and the hindbrain, and by means of preserving free leptin levels. Induction of satiety would protect diabetic women from the hazards of food craving on their blood glucose level during the PMS phase [145]. The main adverse effects of GLP-1RAs are gastrointestinal upset (mainly nausea), headache, and nasopharyngitis. Yet these symptoms do not usually result in drug discontinuation [146].

In the body, GLP-1 is rapidly metabolized and inactivated by the dipeptidyl peptidase IV enzyme (DPP 4). Therefore, DPP4 inhibitors (e.g., sitagliptin, linagliptin, anagliptin, saxagliptin) are approved as T2DM therapies. By preventing the diabetic metabolic hazards, these drugs can ameliorate the DM-related PMS. This group of drugs can in addition suppress oxidative stress, fibrosis, and apoptosis, and they additionally showed a cardioprotective and renal protection power [147]. DPP4 substrates were found to mediate stress, anxiety, depression, and schizophrenia. Thus, the anti-inflammatory and pleiotropic actions of the DPP4 inhibitors could ameliorate the PMS pathophysiology as well [148, 149]. In support of these postulations, sitagliptin was suggested as an alternative to metformin in PCO patients who are intolerant to metformin [150]. These findings raise the hope that DPP4 inhibitors could attenuate some PMS etiologies and have a positive impact on mood disorders, which can help to minimize the mood swings reported in PMS.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase enzymes are located in the brush border of the enterocytes and are greatly responsible for hydrolyzing non-absorbable oligosaccharides and polysaccharides into monosaccharides that can be easily absorbed. The alpha-glucosidase inhibitors (acarbose, miglitol, and voglibose) are pseudo-carbohydrates that can competitively and reversibly inhibit these intestinal enzymes to decrease the postprandial glucose load. Acarbose is poorly absorbed and is excreted unchanged in stool, with up to 30% undergoing metabolism primarily via fermentation by the colonic microbiota [151]. Similarly, voglibose is slowly and poorly absorbed and is rapidly excreted in stool [152]. In contrast, miglitol is completely absorbed from the gut and eliminated by the kidneys [153].

The alpha-glucosidase inhibitors by restoring the normal glucose tolerance can assist in reducing the diabetic-related complications, particularly those that can be considered PMS-related. Acarbose, in addition, appears to have some additive extra-antidiabetic effects when compared to miglitol and voglibose. Acarbose was found to be able to stabilize carotid plaques, improve lipid profile, and reduce inflammation. An RCT, conducted by Ciotta et al. [154] on 30 normally weighting PCOS patients, showed that eight patients who were treated by acarbose resumed their normal menstrual cycles with a significant decrease in the acne/seborrhea score. This clinical improvement was linked to significant declines in the insulin response to glucose load and an additional improvement in LH, total testosterone, and androstenedione levels. There was a significant increase in the serum concentrations of the sex hormone binding globulin as well. Notably, prolactin, 17-hydroxyprogesterone, dehydroepiandrosterone sulphate, and FSH serum concentrations did not show any significant changes. In the same context, Tuğrul et al. [155] stated that acarbose treatment significantly decreased basal insulin concentration, LH/FSH ratio, total testosterone, very low-density lipoprotein (VLDL), and triglyceride levels, with a significant enhancement in HDL level [156]. These effects can not only improve diabetic control and guard against diabetic complications but also may improve the hormonal profile in susceptible PMS-PCO patients.

By interfering with the degradation of complex carbohydrates into glucose, alpha-glucosidase inhibitors will eventually increase the amount of the undigested carbohydrates delivered to the colon. While these complex carbohydrates are then broken down by bacteria in the colon, causing some gastrointestinal side effects such as flatulence (78% of patients) and diarrhea

(14% of patients), these complex carbohydrates in fact favor the growth of the beneficial gut microbiota instead of the harmful strains. This selective action will guard against gut dysbiosis and results in decreasing the systemic inflammatory cytokines levels in patients with diabetes and increasing the butyrate levels [157, 158].

Sodium-Glucose Transporter-2 (SGLT2) Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors work as anti-diabetic drugs through enhancing glucosuria. Dapagliflozin was the first SGLT2 inhibitor to be approved for the treatment of T2DM in Europe in 2012. Then followed the approval of canagliflozin, empagliflozin, and tofogliflozin [159]. SGLT2 inhibitors act on Na^+-glucose cotransporters present in the apical membrane of the early proximal tubules of the kidney where the bulk of glucose uptake occurs [160]. They do not cause hypoglycemia unless combined with insulin secretagogues, especially sulfonylureas [161]. Although this hypoglycemia is not confined to the luteal phase, they may induce PMS-like symptoms.

SGLT2 inhibitors showed an anti-inflammatory potential through different mechanisms. They reduce hyperglycemia and sequentially inhibit glucotoxicity-mediated inflammation, such as endothelial dysfunction and oxidative stress. By facilitating glucosuria, SGLT2 reduces hyperuricemia and decreases the insulin/glucagon ratio, where the latter enhances ketonemia and the associated release of the pro-inflammatory cytokine. SGLT2 inhibitors support the activation of the eNOS, which mediate their cardiac and renovascular protective effects [162].

There is no evidence that SGLT2 inhibitors affect sex hormones, however there is a hypothesis that weight loss associated with SGLT2 inhibitors, particularly canagliflozin, may reduce aromatase activity, which may lower the production of estradiol due to the decreased fat tissue mass [163].

The diuretic effect of SGLT2 inhibitors made them the anti-diabetic drugs of choice for T2DM with heart failure. This action may show advantage in PMS women with fluid retention [164]. In addition, there is evidence that SGLT2 inhibitors have a sympatholytic activity. Although the mechanism of sympathetic inhibition with SGLT-2 inhibitors is not fully understood, it might be of a great benefit in patients with diabetes and PMS to alleviate the sympathetic derived anxiety disorder [165]. Obviously, improving diabetic control would also alleviate the speculated impact of DM on the PMS pathogenesis.

CONCLUSIONS

Diabetes can affect sex hormones, serotonin, GABA, GM, and several inflammatory markers, which can exaggerate PMS symptoms. Some PMS symptoms such as food craving may render the DM control challenging. Hypoglycemia and PMS share some common manifestations and necessitates experts' management. Antidiabetic drugs might improve PMS symptoms through achieving the targeted glucose level, ameliorating inflammation, and relieving the diabetic burden on PMS. Additional benefit is expected with metformin, GLP-1RAs, and DPP4 inhibitors that stimulate satiety and/or cause weight reduction. Metformin, glitazones, and, to a lesser extent, the GLP-1RAs, offer the advantage of improving symptoms of depression, while alpha glucosides inhibitors have a favorable impact on GM. Meanwhile, some drawbacks of these drugs, such as the effect of glitazones on increasing fluid retention, or risk of hypoglycemia and hyperinsulinemia with insulin and insulin secretagogues, require special attention, as they can potentiate PMS severity. Comprehensive and well-designed studies are needed to validate these hypotheses, taking into consideration the differences in the PMS etiology and manifestations and the psychological background of each patient.

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Declarations

Conflict of Interest. Omnia Azmy Nabeh, Alaa Amr, Aml Medhat Faoosa, Eshraka Esmat, Alaa Osama, Amira Samy Khedr, Basma Amin, Alaa I. Saud, and Soha Aly Elmorsy declare that they have no conflicts of interest.

Ethics Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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