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Beyond Pregnancy: The Role of Progesterone Deficiency and Fluctuations in Women's Health Disorders

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ABSTRACT

Progesterone is a steroid hormone that plays a crucial role in regulating the menstrual cycle. A deficiency, often called Luteal Phase Defect (LPD), can lead to pregnancy complications, but also other symptoms. Patients with progesterone deficiency may have short menstrual cycles, irregular menstruation, and abnormal vaginal bleeding. Furthermore, not only a deficiency but also fluctuations in progesterone levels can negatively impact overall health, including brain function. It is still being examined how this hormone affects emotion processing and mood disorders. Effectively treating diseases related to progesterone levels requires looking at the person's whole clinical condition. Therapy may not only rely on progesterone substitution and may not always be satisfactory for the patient. This is an issue that warrants further attention, as our understanding remains insufficient.

Keywords: Progesterone, Luteal Phase Defect, menstrual irregularities, women's mental health, quality of life.

1. INTRODUCTION

Steroid hormones form a diverse group, which includes mineralocorticoids, glucocorticoids, androgens, estrogens, and progestogens. They are mainly produced in the adrenal cortex, ovaries, and testes. Despite their different roles, all steroid hormones originate from cholesterol. Progesterone is synthesized in two enzymatic steps starting directly from cholesterol itself (Taraborrelli, 2015). The corpus luteum in the ovary is the primary site of production. Other tissues, such as the adrenal glands, placenta, and brain, can contribute, though generally in smaller amounts (Stocco, 2001).

Progesterone is best known for its role in the menstrual cycle, although its effects go beyond reproduction. The menstrual cycle is broadly classified into four different phases: menstruation, the follicular phase, ovulation, and the luteal phase. In the first two phases, progesterone levels are kept low. The progesterone effect is most pronounced during the luteal phase, which typically occurs in a regular

menstrual cycle from 11 to 17 days. The luteal phase immediately ensues after ovulation, by which time the Graafian follicle ruptures and forms the corpus luteum. If the luteal phase is shorter than 10 days, it may be considered luteal phase deficiency (LPD). However, there is no consensus on the time criterion, as some studies suggest limits of 9 or 11 days.

Progesterone production in the corpus luteum depends entirely on ovulation. In cycles without ovulation, as often occurs in polycystic ovary syndrome (PCOS), production may be insufficient (Levy et al., 1980). This deficiency may cause LPD, a disorder in which it is difficult to become pregnant and maintain pregnancy (Jones, 1976). In a non-pregnant female, progesterone is a primary preparatory hormone. This transforms the endometrium from the proliferative phase to the secretory phase. This prepares it in case a blastocyst is implanted (Taraborrelli, 2015). Low progesterone might cause irregular or altered menstrual cycles that may induce typical uterine bleeding. This phenomenon significantly impacts overall well-being (Jewson et al., 2020).

Additionally, progesterone acts as a neurosteroid: acting directly on brain receptors, it participates in regulating and modulating mood (Stocco, 2001). Altered progesterone signaling has been theorized in premenstrual dysphoric disorder (PMDD), where cyclical hormone fluctuations seem to contribute to significant mood disturbances. The treatment of progesterone imbalance remains a complex clinical issue. Even though hormone therapy is used at times, it is not obligatory. Current research suggests that vitamin D may have actions that are redundant with those of progesterone, particularly in relation to reproductive and immune function. This overlap is noteworthy because it opens potential avenues for therapy and highlights the need for further investigation in future studies (Monastra et al., 2018).

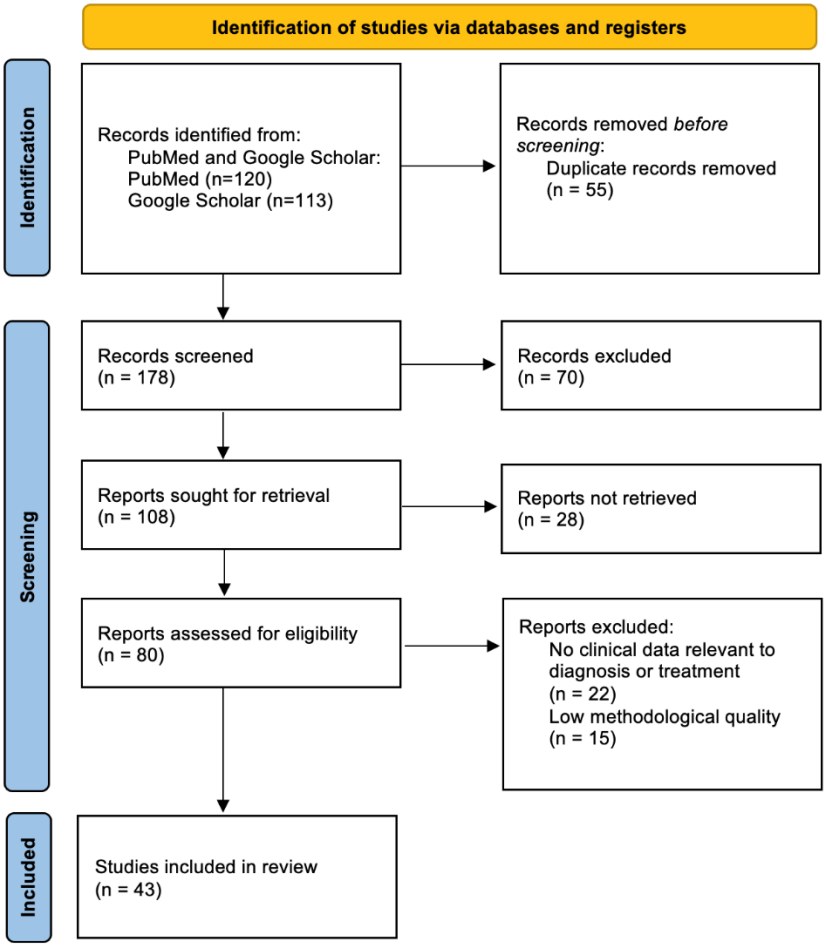

Figure 1: PRISMA flowchart

2. REVIEW METHODS

Literature search included the use of the keyword 'progesterone' in combination with the phrases 'deficiency', 'symptoms', 'physiology', and 'treatment'. These search terms were applied in the databases PubMed and Google Scholar. We included both review articles and

clinical trials in the selection. We restricted the time frame of the published articles to the years January 2000 – March 2025 and included some historical publications if we judged them to help understand the matter. We initially screened 178 articles, from which 80 were assessed for eligibility. Out of those, 37 were not satisfactory in any regard and thus excluded, whereas the remaining 43 were judged relevant and useful (Figure 1). All publications included in this review were in English.

3. RESULTS & DISCUSSION

Physiology of Progesterone

Synthesis

Progesterone is produced in the mitochondria of the corpus luteum in the ovaries, with the conversion of cholesterol into pregnenolone by cytochrome P450scc. Pregnenolone is then converted into progesterone through the action of 3β-hydroxysteroid dehydrogenase/isomerase (Karpov et al., 2024). It is also synthesized locally in the brain, where cholesterol is converted to pregnenolone and then to progesterone by the same key enzymes. This occurs in neurons and glial cells, such as astrocytes and oligodendrocytes. Unlike in other tissues, brain production of progesterone depends on local neural needs, not hormonal regulations (Schumacher et al., 2012).

Role of progesterone in the menstrual cycle and in the brain

Progesterone is widely considered to be the crucial hormone in establishing and sustaining early pregnancy. Its primary function is to prepare the uterine lining for implantation, but it also helps to maintain the pregnancy once the implantation has taken place. To achieve this, the endometrium must shift out of the proliferative phase and into the secretory phase. During this stage, the glands in the lining release nutrients and growth-promoting factors that are necessary for the embryo to develop properly. At the same time, progesterone changes the behavior of several proteins and signaling molecules, essentially reprogramming the endometrium so that implantation can occur. Another role, which tends to get less emphasis but is still critical, is its ability to reduce uterine contractions; in doing so, it lowers the chance of the embryo being expelled too early. In short, progesterone reshapes the uterine environment so that implantation and early gestation are possible (Young and Lessey, 2010).

If implantation never occurs, the corpus luteum regresses typically within nine to eleven days. The exact mechanism remains unknown, but the reduced effect of luteinizing hormone (LH), combined with the influence of prostaglandins and specific cytokines, is likely involved (Filicori et al., 1984; Taraborrelli, 2015). As the corpus luteum degenerates, progesterone production levels drop rapidly. This sudden shift triggers the shedding of the uterine lining, a process known as menstruation. Progesterone withdrawal causes tissue swelling, greater permeability of blood vessels, and an influx of immune cells, which resemble a local inflammatory response. On a molecular level, enzymes like matrix metalloproteinases (MMPs) become active, while inflammatory mediators such as COX-2, prostaglandins, and interleukins are produced in larger amounts. Ultimately, all those changes lead to the shedding of the endometrial lining (Critchley et al., 2020).

Progesterone acts through nuclear receptors found in regions like the cortex, hypothalamus, and pituitary, and through non-genomic mechanisms. Its neuroactive metabolites, such as allopregnanolone (ALLO), act on GABA receptors, which affect mood and anxiety. Additionally, it has been demonstrated that the expression of β-adrenergic receptors in the cortex is enhanced by progesterone. This alteration may influence emotional responses and cognitive processes involved in learning (Mani and Oyola, 2012). We need to emphasize, in particular, that all these actions are most effective during the luteal phase, when progesterone levels are at their maximum. High levels observed during this phase have been linked to better emotional memory, and it is most likely that this results in greater activity in the amygdala and the anterior cingulate cortex, both regions associated with emotional processes. These processes could be involved in the onset of mood disorders such as premenstrual dysphoric disorder (PMDD). Inversely, results concerning cognition were less consistent among different studies. Still, the cumulative evidence suggests that progesterone plays a significant role in emotional reactivity and, by extension, in women's mental health more broadly (Sundström-Poromaa, 2018).

Progesterone deficiency in non-pregnant women

Diagnostic Challenges and Controversies

Progesterone deficiency might be just one among various mechanisms of luteal phase defect. In other instances, the fault is not as simple. Sometimes this condition arises not because the ovaries are not producing enough hormones, but because the endometrial response is deficient even when progesterone levels are normal. For example, the endometrium may be unresponsive to progesterone,

which can affect fertility and the menstrual cycle (Burney et al., 2007). However, this paper aims to examine the relationship between progesterone and mental health. Therefore, the discussion will be restricted to the aspect of progesterone's influence on mental well-being.

Progesterone serum levels are commonly used to assess luteal function, with levels above three ng/mL generally indicative of ovulation. But is one measurement sufficient to represent luteal function? Considering the pulsatile nature of progesterone secretion as well as significant intra-cycle variation, one random measurement is seldom enough to define luteal adequacy. To improve diagnostic accuracy, integrated luteal values of progesterone have been proposed for use, whereby daily values are summated to provide a calculation that is indicative of a luteal phase defect when under 80 ng/mL. Another proposed diagnostic criterion is to have three measurements between luteal days 5–9 that sum up to less than 30 ng/mL. None of these alternatives is, however, clinically substantiated nor in practice use (Practice Committees of the American Society, 2021). This suggests that progesterone deficiency is not easily diagnosable, as is the universally proposed criterion to apply in assessing this.

Quality of Life in Women with Menstrual Disorder

Quality of life (QoL) refers to the subjective feeling that one possesses regarding one's position in life, compared to culture and value systems, physical health, state of mind, level of independence, social contacts, and belief in oneself. Interruptions in the progesterone secretion, as expounded above, can cause short cycles, irregular menstrual cycles, as well as abnormal uterine bleeding - disorders that are included in menstrual disorders that significantly influence the level of comfort as well as general health in women. Menstrual disorders can influence various QoL domains both physically and psychologically.

Cross-sectional surveys were conducted among Japanese female students at universities, in which the relation between menstrual health and psychosocial stress has been explored. Two hundred twenty-one students completed a questionnaire to evaluate menstrual disturbance as well as lifestyle parameters. Psychosocial stress was assessed with the use of the Inventory to Measure Psychosocial Stress (IMPS). Many respondents experienced premenstrual symptoms (79%), menstrual pain (79%), and - most importantly in this regard - irregular menstrual cycles (63%). Above all, increased stress levels correlated significantly with the occurrences of these menstrual disturbances. The authors therefore postulated that psychosocial stress has the potential to relate to menstrual disorders among young women (Yamamoto et al., 2009).

In addition to the physiological manifestations, menstrual irregularities may also affect thinking, behavior, and academic performance (Gurvich et al., 2018). Studies have found that women with irregular menstrual cycles are characterized by poorer academic performance, as well as lower grades. In a cross-sectional study conducted at Debre Berhan University, students with irregular cycles were noted to have significantly lower average grades compared to those with regular cycles. Difficulty in concentration was also reported among irregularly cycled students, indicating that menstrual irregularity may correlate with poor academic performance (Demeke et al., 2023).

Alkathem et al., (2024) also bring to light another health challenge encountered by people who have menstrual disorders: the massive effect that irregular cycles have on the quality of life, including social connections. As many as 47.6% of respondents reported adverse social associations altered by menstrual irregularity.

These findings, collectively, underline the multifaceted impact of menstrual disorders on the female quality of life, bearing not only on psychological health as well as performance in school, but also on interpersonal connections. This research suggests that menstrual health is a broader public health phenomenon with applications that extend beyond gynaecology into mental health, education, and social performance.

The Direct Impact of Progesterone and Its Metabolite Allopregnanolone on Mental Health. The World Health Organization (WHO) has defined mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and can contribute to his or her community." Hormonal fluctuations, specifically the changes that involve progesterone, are found to manifest as significant predictors in emotional stability as well as mood regulation in females.

PMDD is characterized by dramatic mood swings, depressed mood, anxiety, overall irritability, and even somatic symptoms. To be diagnosed with PMDD, these episodes must happen in the luteal phase and resolve in three days after the onset of menstrual bleeding (Grady-Weliky, 2003). A significant number of studies attribute this disorder to changes in progesterone, or rather in its neuroactive metabolite, ALLO, which interacts with gamma-aminobutyric acid (GABA) receptors in the brain. GABAergic transmission plays a crucial role in calming and stabilizing mood (Kalueff and Nutt, 2007).

In the case study by Hantsoo and Epperson (2020), it was demonstrated that in women with PMDD, the drop in progesterone and ALLO in the late luteal phase is sharper compared to healthy individuals. Preclinical studies have proved that rapid diminution in ALLO (as well as progesterone) can cause a change in subunit composition in GABA receptors that impairs these neurons' adaptivity to changing levels of neurosteroids. Consequently, in the brain in PMDD, these receptors are ineffective in exerting appropriate inhibitory control that may underlie emotional over-reactivity as well as increased irritability. The body of studies points to the fact that in this disease, the primary pathology is not in absolute levels of progesterone but like the change in these levels.

Another good illustration of the role that the sudden decrease in progesterone can have on mental health is that of "maternity blues," a disturbance in mood that occurs in many women in the first days postpartum. Though generally mild and self-limiting, in others, it can precede the onset of postpartum depression. Studies have demonstrated that those women who have more severe maternity blues symptoms tend to have elevated levels of progesterone in pregnancy, with a marked decrease thereafter. Here again, the important factor doesn't seem to be the level of progesterone per se, but rather the rapid change in hormones. Emphasis has again gone to progesterone's neuroactive metabolite allopregnanolone, which acts on GABA receptors and has calming, anxiolytic actions. A sudden postpartum decrease in these substances may impair GABAergic transmission and provide a contributory factor to mood lability. Consequently, newer studies have focused more attention on the functions of these metabolites as anti-prolactin precursors in preventing or treating postpartum affective disorders (Harris et al., 1994).

The overview of the evidence suggests the influence of progesterone and its neuromodulatory metabolite on the mental health of females. It is possibly the rapid change rather than the levels in themselves of the hormone that can lie underneath disruptions in mood like PMDD and pregnancy blues. This body of research suggests the relevance of hormonal dynamics in the etiology of certain mood disorders and points towards additional research into GABA-modulating therapies targeted against progesterone metabolites as promising therapeutic avenues.

Therapeutic challenges

Progesterone substitution

Although it would otherwise be reasonable to treat disorders associated with progesterone through hormone replacement therapy, it is less straightforward. The first stage involves ruling out a different form of medical cause, such as a thyroid, adrenal, or prolactin-associated hormone disorder, as these can disrupt the luteal phase. Administering progesterone in these cases would be ineffective and is unlikely to provide long-term benefits for the patient. If the conditions have been excluded, hormone substitution may be considered. In the case of LPD caused by a clear progesterone deficiency, supplementation of this hormone is primarily justified in the context of infertility treatment and early pregnancy support (Practice Committee of the American Society for Reproductive Medicine, 2012). For LPD symptoms not related to pregnancy, such as irregular menstruation, current evidence remains limited and inconclusive.

Existing data on the use of progestogens for treating irregular menstrual bleeding associated (particularly with oligo- or anovulation) are limited. There is a lack of randomized controlled trials meeting high methodological standards, which hinders the formulation of strong clinical recommendations. Available findings suggest that short-term use of oral progestogens may reduce the volume and duration of bleeding and may positively influence endometrial histology. However, this effect is not sustained after discontinuation of treatment. Further research is needed, particularly randomized trials comparing different types, doses, and routes of administration of progestogens - both as monotherapy and in combination with estrogen (Hickey et al., 2012).

In the treatment of PMDD, the best-studied and recommended approach is cognitive-behavioral therapy (CBT) for milder symptoms, while serotonergic antidepressants are indicated when symptoms are more severe. Hormonal contraception may also be recommended, although it has been less thoroughly studied in this context (Busse et al., 2009). Progesterone therapy during the luteal phase is not effective (American College of Obstetricians and Gynecologists, 2023). Overall, the treatment of progesterone-related disorders is complex and not yet fully supported by high-quality clinical research.

Vitamin D: A Potential Therapeutic Ally?

Monastra et al., (2018) discussed the analogy between vitamin D and progesterone, providing promising avenues, especially in relation to women's reproductive health. From their study, though historically labeled as a vitamin, vitamin D qualifies as a steroid hormone by virtue of endogenous production, transport through binding proteins, interaction at the level of the nucleus, as well as the capacity to regulate transcription of genes. Its biologically active form, calcitriol ($1,25(OH)_2D$), is nowadays broadly viewed as a hormone per se.

Vitamin D, structurally and functionally, is analogous to classical steroid hormones, such as progesterone. These hormones control the immune system through the induction of anti-inflammatory pathways, the activation of regulatory T cells, and the suppression of pro-inflammatory cytokine production. Within the endometrium, vitamin D promotes key implantation-associated genes such as osteopontin and calbindin, similarly to progesterone in the luteal phase. Vitamin D can also encourage the expression of progesterone in granulosa cells as well as increase the expression of progesterone receptors in immune cells, suggesting mutual interaction (Viganò et al., 2006).

These mechanisms underlie the speculation that vitamin D not only augments but possibly enhances progesterone's actions in the important window of implantation as well as early pregnancy. Although this provides an encouraging insight, more extensive clinical research is required for vitamin D to be considered a real alternative for progesterone in LPD treatment. The key findings of this review are summarized below (Table 1).

Table 1. Key Insights on Progesterone Deficiency and Fluctuations in Women's Health

Focus Area	Summary of Evidence	References
Beyond Reproduction	Progesterone is not only critical for implantation and sustaining pregnancy but also functions as a neurosteroid, influencing mood, cognition, and emotional processing.	Taraborrelli (2015); Stocco (2001); Young and Lessey (2010); Mani and Oyola (2012)
Pathological Consequences	Both deficiency and rapid hormonal shifts are implicated in infertility, abnormal bleeding, PMDD, and postpartum mood disturbances.	Jones (1976); Filicori et al., (1984); Grady-Weliky (2003); Hantsoo and Epperson (2020); Harris et al., (1994)
Diagnostic Ambiguities	Progesterone testing lacks standardized criteria. Single serum values are unreliable due to pulsatile secretion; alternative cumulative measures exist but are not clinically adopted.	Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility (2021); Filicori et al., (1984)
Impact on Daily Functioning	Menstrual irregularities reduce quality of life through pain, stress, impaired concentration, reduced academic performance, and altered social interactions.	Yamamoto et al., (2009); Gurvich et al., (2018); Demeke et al., (2023); Alkathem et al., (2024)
Neurobiological Mechanisms	ALLO, a progesterone metabolite, modulates GABA receptors. Rapid declines alter receptor sensitivity and underlie mood instability in PMDD and postpartum disorders.	Kalueff and Nutt (2007); Sundström-Poromaa (2018); Hantsoo and Epperson (2020); Harris et al., (1994)
Therapeutic Evidence	Progesterone supplementation is mainly effective in infertility; its broader efficacy is limited. For PMDD, cognitive-behavioral therapy and SSRIs remain preferred treatments.	Practice Committee of the American Society for Reproductive Medicine (2012); Hickey et al., (2012); Busse et al., (2009); American College of Obstetricians and Gynecologists (2023)
Future Directions	Vitamin D shows overlapping functions with progesterone, particularly in implantation and immune modulation, suggesting a possible therapeutic role pending further trials.	Monastra et al., (2018); Viganò et al., (2006)

4. CONCLUSION

While commonly understood as the principal pregnancy hormone, progesterone is also involved in the health of non-pregnant females. Defects or variations in levels can cause not only infertility but also a variety of non-pregnancy-specific symptoms such as irregular menstrual cycles, diminished quality of life, and impairments in mental as well as social performance. Progesterone's role as a neuromale steroid hormone, as well as emotional-mood regulation, helps to define the significance of hormonal balance to feminine mental health.

The diagnosis of progesterone deficiency is still uncertain, partially due to the pulsatile nature of progesterone secretion, as well as due to the nonexistence of diagnostic criteria. The treatment is not clear-cut either. It is not always based on hormone replacement therapy, and treatment should be individualized for the given clinical case. Promising studies suggest that vitamin D may have a role in the treatment of progesterone deficiency as an intensifier or regulator of the action of progesterone, though clinical confirmation is needed.

There is a great need to deepen medical and public awareness of the non-pregnancy consequences of progesterone imbalance, as well as the importance of cross-disciplinary care for the hormonal health of women: gynecology, endocrinology, psychiatry, and public health in tandem.

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Author contributions

Natalia Skrzypska contributed to the study design, coordinated the writing process, and led the development of the final manuscript.
Hubert Ziembicki was responsible for background research, clinical content input, and refinement of the discussion section.
Justyna Wróblewska supported data interpretation, helped organize the structure of the paper, and reviewed the final draft for consistency.
Paulina Wasilewska performed the initial literature screening and contributed to the introduction and conclusion sections.
Olga Wojtczak assisted with referencing and table preparations.
Kacper Zagaja assisted in literature analysis, handled formatting and technical editing, and ensured adherence to submission guidelines.

Informed consent

Not applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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