Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 09 May 2026
Revised 24 June 2026
Accepted 04 July 2026

Natural Resources for Human Health 2026, Vol. 6 (11s): 1291–1305

KEYWORDS:
Allopregnanolone; Hormone sensitivity; Menopause; Perimenopause; Postpartum depression; Premenstrual dysphoric disorder; Premenstrual syndrome; Reproductive psychiatry.

Not Broken, Just Sensitive- A Systematic Review of Hormones, Mood and the Female Mind Across the Reproductive Lifespan

Dr. Arijit Mazumdar

Assistant Professor, Department of Physiology P.A. Sangma International Medical College (PIMC), University of Science and Technology Meghalaya (USTM) Ri-Bhoi District, Meghalaya, India

ABSTRACT:

Background: Across the reproductive lifespan, women repeatedly describe a lived experience that clinical medicine has been slow to validate: predictable windows of time in which mood, sleep, and cognition shift in step with reproductive hormones, followed by a return to baseline once those hormones stabilise. For decades this experience was dismissed as excess emotionality; contemporary neuroendocrinology instead points to differential brain sensitivity to entirely normal hormonal fluctuations.

Objective: To synthesise the evidence for a hormone-sensitivity model of mood across four windows — the menstrual cycle (premenstrual syndrome and premenstrual dysphoric disorder), pregnancy and the postpartum period, the perimenopausal transition, and menopause — and to critically evaluate what this model does and does not explain.

Methods: A structured search of PubMed and Google Scholar (inception to September 2026) covering neuroendocrinology, reproductive psychiatry, and clinical guideline literature was synthesised narratively, anchored by landmark experimental studies establishing the sensitivity paradigm.

Results: Convergent evidence from ovarian-suppression and hormone add-back trials, allopregnanolone-GABA-A receptor pharmacology, and cellular transcriptomic studies of the ESC/E(Z) gene complex indicates that affected women have normal circulating hormone levels but an intrinsically altered neural and cellular response to their fluctuation. This sensitivity framework explains premenstrual dysphoric disorder, a meaningful subset of postpartum depression, and perimenopausal depressive episodes, and has already yielded targeted neurosteroid therapeutics. Conclusion: Hormones do not explain every difficult emotion in a woman's life, and this review argues explicitly against over-medicalising ordinary distress. But for a biologically definable subset of women, recognising heightened hormone sensitivity, rather than hormone abnormality, reframes a century of dismissal into a testable, treatable clinical model.

1. INTRODUCTION AND BACKGROUND

1.1. A conversation clinicians hear every day

"Doctor, I don't understand what happens to me every month." Some version of that sentence opens countless consultations in gynaecology, primary care, and psychiatry clinics worldwide. A patient describes ten days of irritability, tearfulness, and a mind that feels, in her words, "on fire," followed by the arrival of her period and a return to feeling like herself again. She often asks, almost apologetically, whether she is becoming mentally unstable. The honest clinical answer is rarely that simple, and it

is rarely the one she expects: sometimes the problem is not that a woman has changed, but that her biology moves through genuinely different states — and some brains respond to those states far more intensely than others.

That distinction matters enormously, and it sits at the centre of this review. It is not the same claim as "it's just hormones," a phrase that has done real damage over the years by flattening complex psychological experience into a biological shrug. Nor is it the opposite claim, that mood symptoms tied to the reproductive cycle are simply psychological and therefore not "real" in a medical sense. The evidence assembled here supports a third, more precise position: across several distinct windows of a woman's reproductive life — the luteal phase of the menstrual cycle, the weeks after childbirth, the perimenopausal transition, and menopause itself — the brain is exposed to genuine, measurable hormonal change, and a subset of women appear to carry a biological sensitivity to that change that other women do not.

1.2. From "hysteria" to hormone science: a brief history of dismissal

The word "hysteria" derives from the Greek hystera, meaning uterus, and for well over two thousand years, Western medicine attributed a huge range of female emotional experience to a supposedly "wandering womb." That theory was medically absurd even by the standards of its own era, but its cultural residue proved remarkably durable. Well into the twentieth century, cyclical mood change in women was still routinely framed as a character flaw — too emotional, too sensitive, too moody — rather than as a phenomenon worth serious biological investigation. Premenstrual syndrome itself was not formally named in the medical literature until the 1930s, and premenstrual dysphoric disorder did not receive formal psychiatric recognition until the DSM-5 in 2013, despite clinical descriptions of severe premenstrual mood change dating back decades earlier.

What changed the conversation was not a shift in attitude so much as a shift in method. Beginning in the 1990s, a small number of research groups — most notably David Rubinow and Peter Schmidt at the US National Institute of Mental Health — designed experiments that could finally distinguish two very different hypotheses: that symptomatic women had abnormal hormone levels, or that they had a normal hormonal cycle but an abnormal response to it. The answer, established with remarkable clarity and replicated many times since, favoured the second hypothesis almost completely. That single finding reorganised an entire field, and it is the thread this review follows across every reproductive life stage that comes after it.

It is worth being honest about why this took so long to establish properly. Studying hormone-mood interactions rigorously requires controlling for the very thing that makes the biology interesting in the first place, a moving hormonal target, which is technically and ethically demanding: it requires GnRH-agonist ovarian suppression, carefully blinded hormone add-back, and willing participants prepared to tolerate weeks of induced menopausal-like symptoms for the sake of a research question. Funding streams for women's reproductive mental health research have also historically lagged behind funding for conditions affecting both sexes equally, a disparity that has only partially narrowed in recent decades. Both factors, not merely scientific difficulty alone, help explain why a condition affecting a comparable proportion of women to generalised anxiety disorder took until the twenty-first century to receive a proper mechanistic explanation.

1.3. Objectives of this review

This review sets out to do four things: lay out the shared neuroendocrine machinery, principally the hypothalamic-pituitary-gonadal axis, the serotonergic system, and the neurosteroid allopregnanolone acting on GABA-A receptors, that links hormone change to mood across a woman's life; trace the sensitivity hypothesis from its landmark experimental origins through to its molecular and genetic evidence base; apply that framework in turn to premenstrual syndrome and premenstrual dysphoric disorder, perinatal mood disorders, perimenopausal depression, and menopause; and offer a candid, evidence-anchored opinion on where this framework is genuinely useful in clinical practice and where it risks being stretched further than the data actually support.

2. METHODS

2.1. Search strategy and information sources

A structured literature search was conducted across PubMed/MEDLINE and Google Scholar from inception to September 2026, combining the terms "premenstrual syndrome," "premenstrual dysphoric disorder," "hormone sensitivity," "allopregnanolone," "GABA-A receptor," "postpartum depression," "perinatal depression," "perimenopause," "menopause," and "reproductive psychiatry." Reference lists of retrieved articles were hand-searched for additional primary sources, with

particular attention to the experimental studies that established the sensitivity paradigm in each life stage, since these mechanistic studies matter more to the argument of this review than any single prevalence estimate.

2.2. Eligibility criteria

Peer-reviewed original research, systematic reviews, meta-analyses, and clinical guideline documents published in English were eligible. Landmark experimental studies — ovarian suppression and hormone add-back trials, cellular and transcriptomic studies, and pivotal pharmacological trials — were prioritised even where they were not the most recent publication on a given topic, because the argument of this review rests on mechanism, not just on prevalence.

2.3. Data synthesis approach

As with any review spanning multiple distinct clinical syndromes, the evidence base here is heterogeneous by design: randomised controlled trials for pharmacological questions, cellular and molecular studies for mechanism, and epidemiological cohorts for prevalence and risk. This review therefore adopts a narrative-systematic synthesis, organised around reproductive life stage, with the underlying neuroendocrine mechanism treated as the connective thread running through every section rather than as a separate, selected topic.

3. THE NEUROENDOCRINE FOUNDATIONS: HOW HORMONES TALK TO THE BRAIN

3.1. The hypothalamic-pituitary-gonadal axis across the cycle

The menstrual cycle is driven by a tightly choreographed feedback loop. Pulsatile gonadotropin-releasing hormone (GnRH) from the hypothalamus drives follicle-stimulating hormone (FSH) and luteinising hormone (LH) release from the anterior pituitary, which in turn drive follicular development and ovarian steroid production. Estradiol rises through the follicular phase, peaks near ovulation, and after ovulation the corpus luteum begins producing progesterone alongside a second, smaller estradiol peak. If pregnancy does not occur, both hormones fall sharply in the late luteal phase, triggering menstruation and restarting the cycle. None of this is exotic biology — it happens, in broad strokes, the same way in every ovulating woman — but the brain's response to it is where individual women begin to diverge sharply from one another.

3.2. Estrogen, progesterone, and neurotransmitter systems

Estradiol is not a passive bystander in the brain; it actively modulates serotonin synthesis, serotonin receptor density, and serotonin transporter expression, and it shapes dopaminergic reward circuitry as well. Because serotonergic tone is central to mood regulation, and because this is the same neurotransmitter system targeted by most antidepressants, cyclical estrogen change provides a plausible and now well-supported route through which the menstrual cycle can influence mood, appetite, and energy even in women without any diagnosable mood disorder.

3.3. Allopregnanolone and the GABA-A receptor: the master keys

If estrogen's effects on serotonin explain part of the picture, the single most important molecule in this entire review is arguably allopregnanolone, a metabolite of progesterone that acts as a potent positive allosteric modulator of the GABA-A receptor, the brain's principal inhibitory (calming) receptor system. Allopregnanolone levels track progesterone closely, rising through the luteal phase and falling again premenstrually and rising dramatically further during pregnancy before collapsing after delivery. In a brain with typical GABA-A receptor sensitivity, these fluctuations are absorbed smoothly. In a brain with atypical sensitivity, rapid allopregnanolone withdrawal reduces GABA-A receptor responsiveness, chloride influx falls, inhibitory tone on excitatory (pyramidal) neurons weakens, and the clinical result can be anxiety, irritability, and depressed mood appearing in close temporal lockstep with the hormonal shift itself (Kanes, 2023; Mu et al., 2021).

3.4. Why individual brains differ at all

A reasonable question at this point is why any of this would vary meaningfully between individual women in the first place, given that the underlying hormonal cycle itself is broadly similar across ovulating women. Part of the answer lies in GABA-A receptor subunit composition, which can shift in response to sustained neurosteroid exposure in ways that differ between individuals, altering how strongly a given allopregnanolone concentration actually modulates the receptor. Part of it likely lies in serotonin transporter gene variation, which has been associated with differential mood sensitivity to hormonal change in some, though not all, genetic association studies. And part of it, as the next section describes in detail, appears to be a more fundamental, trait-like difference in cellular response to ovarian steroids that is measurable even outside the brain entirely, in

ordinary blood cells grown in a laboratory dish. None of these mechanisms are mutually exclusive, and the current scientific consensus treats them as complementary layers of the same underlying sensitivity rather than as competing explanations.

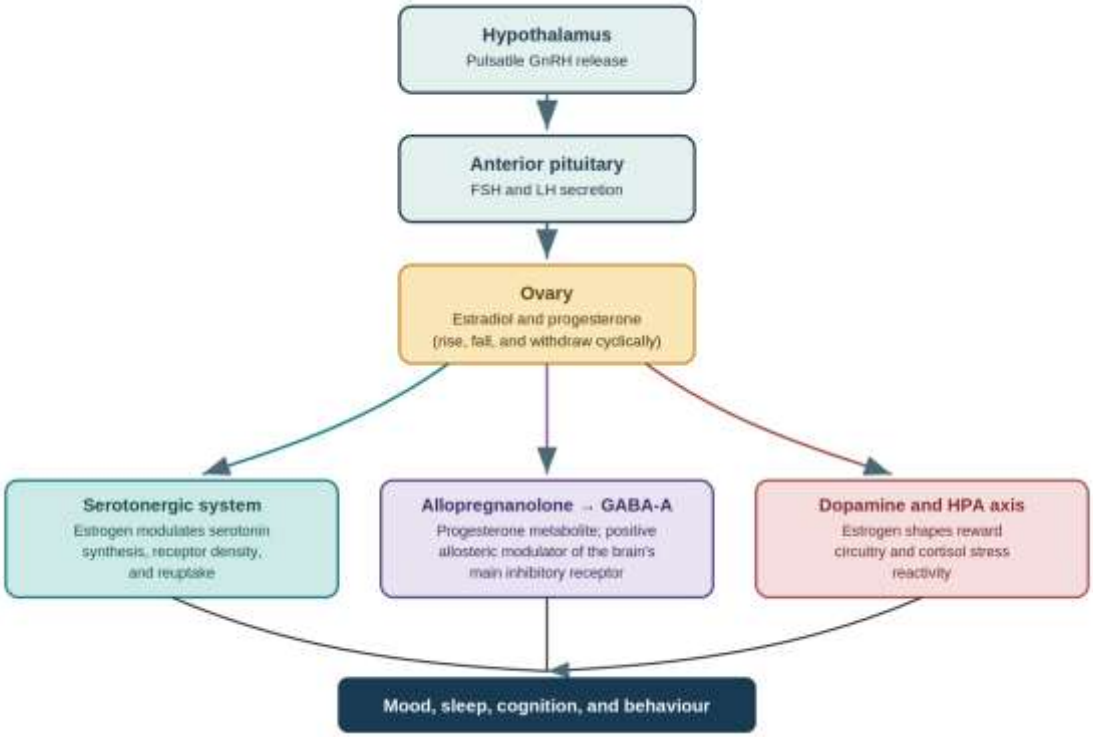

Figure 1. The hypothalamic-pituitary-gonadal axis and its three principal downstream routes to mood, sleep, and cognition.

4. THE SENSITIVITY HYPOTHESIS: WHY SOME WOMEN FEEL IT MORE

4.1. The landmark Schmidt-Rubinow ovarian suppression studies

The experiment that reshaped this entire field was elegantly simple in design, even though it took years to execute properly. Rubinow, Schmidt, and colleagues used a GnRH agonist to chemically suppress ovarian hormone production entirely in women with confirmed premenstrual syndrome and in asymptomatic controls, effectively flattening everyone's hormones to a low, stable baseline. Both groups' symptoms improved on suppression alone. The researchers then "added back" physiological doses of estradiol and progesterone, in a blinded, crossover, placebo-controlled design, to both groups equally. Symptomatic women experienced a return of their mood symptoms during hormone add-back; the asymptomatic controls, receiving the identical hormone doses, did not (Schmidt et al., 1998). Because both groups received the same hormones in the same doses, the study could rule out the simplest explanation, that symptomatic women simply had "too much" or "too little" of something. What differed was not the hormone exposure. What differed was the brain's response to it.

4.2. The ESC/E(Z) gene complex: molecular proof of sensitivity

For nearly two decades, that behavioural finding stood without a clear cellular mechanism to explain it. That changed in 2017, when Dubey, Rubinow, Schmidt, and colleagues at the National Institute of Mental Health compared lymphoblastic cell lines, essentially, immortalised white blood cells grown in culture, from women with confirmed premenstrual dysphoric disorder against cell lines from asymptomatic controls. Under hormone-free conditions, cells from women with PMDD already showed significantly higher expression of most of the thirteen genes making up the ESC/E(Z) complex, an epigenetic gene-silencing system that itself responds to ovarian steroids. When exposed to estradiol and progesterone in culture, the PMDD-derived cells responded completely differently from the control cells (Dubey et al., 2017). In plain terms: the researchers found a measurable, reproducible molecular difference in how PMDD cells are wired to respond to sex hormones, sitting quietly in a blood sample, with no hormones added at all. A related transcriptomic study has since reported a comparable pattern of intrinsically

dysregulated cellular stress-signalling genes in women with a history of postpartum depression (Payne et al., 2023), suggesting this is not an isolated finding confined to one syndrome.

4.3. What "sensitivity" means clinically

None of this means the sensitivity itself is visible on a routine blood test; a woman with severe PMDD will, in almost every case, have entirely normal serum estradiol and progesterone levels (Nevatte et al., 2013). That single fact, counterintuitive as it sounds, is actually the clinically useful takeaway: ordering hormone panels in a woman with classic cyclical mood symptoms is rarely diagnostic, because the biology of the problem was never really about the level of the hormone in the first place. What matters diagnostically is not a number in a lab report but a pattern in time — whether symptoms reliably track the luteal phase, whether they resolve with menstruation, and whether that pattern repeats across cycles. This is precisely the clinical instinct captured, in far more accessible language, by the practising clinician's advice to "notice when symptoms begin, notice when they disappear, notice whether they follow your cycle." That everyday clinical wisdom and this laboratory science are, in the end, describing the same underlying phenomenon from two different vantage points.

5. PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

5.1. Definitions and diagnostic criteria

Premenstrual syndrome (PMS) describes a broad constellation of physical and emotional symptoms — irritability, breast tenderness, bloating, appetite change, low mood — occurring in the days before menstruation and resolving with its onset. Premenstrual dysphoric disorder (PMDD) is a more severe, formally defined subtype, requiring at least five symptoms, including at least one core affective symptom (marked irritability, mood swings, depressed mood, or anxiety), present during the final week before menses, improving within a few days of menses onset, and causing clinically significant impairment in work, school, or relationships (American Psychiatric Association, 2013). Critically, both PMS and PMDD are defined by their timing, not by symptom content alone; the same list of symptoms occurring throughout the cycle, without a clear luteal-phase pattern, points toward a different diagnosis entirely.

5.2. Epidemiology and burden

PMS in some form affects a striking proportion of menstruating women, with pooled global prevalence estimates around 48%, though severity varies enormously (Modzelewski et al., 2024). PMDD, the more severe and clinically significant end of that spectrum, affects an estimated 3 to 8% of women of reproductive age (Halbreich et al., 2003), a prevalence broadly comparable to generalised anxiety disorder or panic disorder. Because PMDD symptoms recur for roughly one week out of every cycle, a woman experiencing it across her reproductive lifespan, spanning some 450 menstrual cycles, accumulates an estimated 8.6 cumulative years of active symptoms, a burden roughly comparable to that of recurrent major depressive disorder (Hantsoo & Epperson, 2020).

Reported prevalence varies somewhat across regions and populations, though this likely reflects diagnostic practice and cultural willingness to report psychological symptoms at least as much as any true biological difference. In many South Asian and other clinical settings, premenstrual mood symptoms are still often normalised as an unavoidable part of womanhood rather than something to raise with a clinician, which likely means the true regional prevalence of clinically significant PMDD is underestimated wherever this normalisation is strongest. This is precisely the same dynamic, understating a real biological phenomenon because it has been culturally folded into ordinary expectation, that this review's introduction described in the context of historical dismissal more broadly, and it is a pattern worth actively watching for in everyday clinical practice, not only in epidemiological studies.

5.3. Pathophysiology

As established in Section 4, current evidence indicates that women with PMS and PMDD have hormone levels indistinguishable from asymptomatic women; what differs is central nervous system sensitivity to the normal luteal-phase decline in allopregnanolone and its effects on GABA-A receptor function (Hantsoo & Epperson, 2020; Stat Pearls, 2026). A parallel, and likely interacting, mechanism involves serotonergic dysregulation, which is consistent with the clinical observation that selective serotonin reuptake inhibitors (SSRIs) are effective in PMDD even when dosed intermittently, only during the luteal phase, rather than continuously (Yonkers et al., 2008). More recent work has also implicated low-grade inflammation and epigenetic

modification of hormone and neurotransmitter pathways as contributing, rather than competing, mechanisms (Comasco & Sundström-Poromaa, 2022).

5.4. Treatment approaches

Effective PMDD treatment follows directly from this mechanistic understanding. Continuous or luteal-phase-only SSRIs remain first-line pharmacotherapy and, notably, tend to work within days rather than the weeks typically required for major depressive disorder, a rapid response consistent with a direct effect on neurosteroid metabolism rather than a purely monoaminergic antidepressant mechanism (Yonkers et al., 2008). Combined oral contraceptives, particularly those containing drospirenone with a shortened hormone-free interval, can suppress the ovulatory cycle and its associated hormonal swings for some women, while GnRH agonists, chemically replicating the very ovarian suppression used in the original Schmidt-Rubinow experiments, remain an option for severe, treatment-resistant cases (Nevatte et al., 2013). Cognitive behavioural therapy, exercise, and structured symptom tracking round out a genuinely biopsychosocial approach, one that treats the biology as real without treating it as the only thing that matters.

Feature	PMS	PMDD
Approximate global prevalence	~48% (any symptoms)	3–8% (diagnostic threshold)
Core requirement	Physical and/or emotional symptoms, luteal phase	≥5 symptoms incl. ≥1 core affective symptom
Functional impairment	Variable, often mild	Required for diagnosis
Hormone levels	Normal	Normal
Proposed mechanism	Serotonergic and neurosteroid sensitivity (milder)	Marked allopregnanolone-GABA-A sensitivity
First-line treatment	Lifestyle measures, symptomatic relief	SSRIs (continuous or luteal-phase), hormonal suppression

Table 1. Premenstrual syndrome versus premenstrual dysphoric disorder.

6. THE PERINATAL WINDOW: PREGNANCY AND POSTPARTUM

6.1. Hormonal turbulence of pregnancy

Pregnancy involves the single largest hormonal transformation a human body ever undergoes outside of puberty itself. Estradiol and progesterone rise progressively, peaking between roughly the 32nd and 40th gestational weeks at levels many times higher than any point in the non-pregnant cycle (Bloch et al., 2003). Alongside the excitement of impending motherhood, this hormonal surge, combined with very real physical, financial, relational, and identity-level changes, commonly brings antenatal anxiety, altered sleep, and shifts in body image. None of this automatically constitutes a disorder; distinguishing normal adaptation from clinically significant antenatal depression or anxiety again depends heavily on severity, persistence, and functional impact rather than on the mere presence of difficult emotion.

Antenatal depression deserves a specific mention here, since it is often overshadowed in both research and public conversation by its postpartum counterpart, despite affecting a broadly comparable proportion of pregnant women and carrying its own independent risks, including preterm birth and low birth weight when left untreated. Part of the reason antenatal depression receives less attention may be structural: many depressive symptoms, fatigue, appetite change, altered sleep, overlap substantially with the ordinary physical experience of pregnancy, making screening tools calibrated for the non-pregnant population less reliable and clinicians understandably more hesitant to label physical pregnancy symptoms as psychiatric ones. This is a genuine diagnostic challenge rather than a reason to avoid screening altogether, and validated pregnancy-specific instruments exist precisely to address it.

6.2. Postpartum depression: epidemiology and risk

Postpartum depression (PPD) is common, affecting an estimated 11 to 17% of women globally, with meaningfully higher rates reported in low- and middle-income countries and in some regions exceeding 20% (Fiala et al., 2023; Song, 2025). It typically presents with sadness, guilt, worthlessness, sleep disturbance beyond what is expected from newborn care alone, anxiety, and anhedonia, and in its more severe presentations, suicidal ideation, and it is distinct both from the mild, self-limiting "baby blues" affecting a majority of new mothers in the first two weeks, and from the rare but genuinely psychiatric emergency of postpartum psychosis discussed below.

Risk factors for PPD extend well beyond the hormonal mechanism that is this review's primary focus, and a responsible clinical picture has to hold both layers at once. A personal or family history of depression, a difficult or traumatic delivery, lack of social support, unplanned pregnancy, and infant health complications all independently raise risk, often substantially more than any single measurable hormonal parameter does on its own. This is one of the clearest illustrations in this entire review of why a purely biological framework, however mechanistically satisfying, cannot fully substitute for a broader psychosocial assessment; the neurosteroid story explains a great deal about why the postpartum period specifically is a window of vulnerability, but it does not explain, by itself, why one particular woman within that window becomes unwell while her neighbour, facing an ostensibly similar hormonal trajectory, does not.

6.3. The withdrawal hypothesis and neurosteroid therapeutics

The precipitous fall in estradiol and progesterone within 24 to 48 hours of delivery, illustrated in Figure 2, is one of the most abrupt endocrine transitions the human body ever experiences, and it drives an equally abrupt collapse in allopregnanolone. The central question in perinatal psychiatry mirrors the one already answered for PMDD: why do some women tolerate this withdrawal without incident while others develop major depression in response to it? The most compelling recent evidence again points to differential cellular sensitivity rather than an abnormal hormonal trajectory. A 2023 transcriptomic study modelling pregnancy-like hormone exposure and withdrawal in lymphoblastoid cell lines found intrinsically dysregulated stress-signalling gene networks in cells derived from women with a history of PPD, a striking cellular parallel to the ESC/E(Z) findings in PMDD (Payne et al., 2023).

This mechanistic understanding has already produced real, approved medicines rather than remaining a laboratory curiosity. Brexanolone, an intravenous formulation of allopregnanolone itself, was approved by the US FDA in 2019 as the first medication specifically indicated for PPD, and zuranolone, an oral synthetic neurosteroid with a similar mechanism, followed in 2023, offering a considerably more accessible route to the same GABA-A-targeted effect (Kanes, 2023; Deligiannidis et al., 2023). Both drugs act rapidly, often within days, which is itself indirect evidence for the underlying excitation-inhibition, GABAergic mechanism, since conventional antidepressants acting through monoamine systems typically take several weeks to show comparable benefit (Meltzer-Brody, 2023).

6.4. Postpartum psychosis: a psychiatric emergency

Postpartum psychosis is far rarer than PPD, affecting roughly 1 to 2 per 1,000 deliveries, but it is a genuine psychiatric emergency, presenting with rapid-onset confusion, delusions, hallucinations, or severe mood disturbance, typically within the first two to four weeks postpartum, and carrying a real risk of harm to mother or infant if untreated (Bergink et al., 2016). Unlike the more nuanced, spectrum-based framing that applies to PMS, PMDD, and typical PPD elsewhere in this review, postpartum psychosis requires urgent psychiatric admission and treatment without delay; it is not a condition to be managed by symptom tracking or watchful waiting, and any suggestion of it warrants immediate escalation.

Natural Resources for Human Health
eISSN: 2583-1194

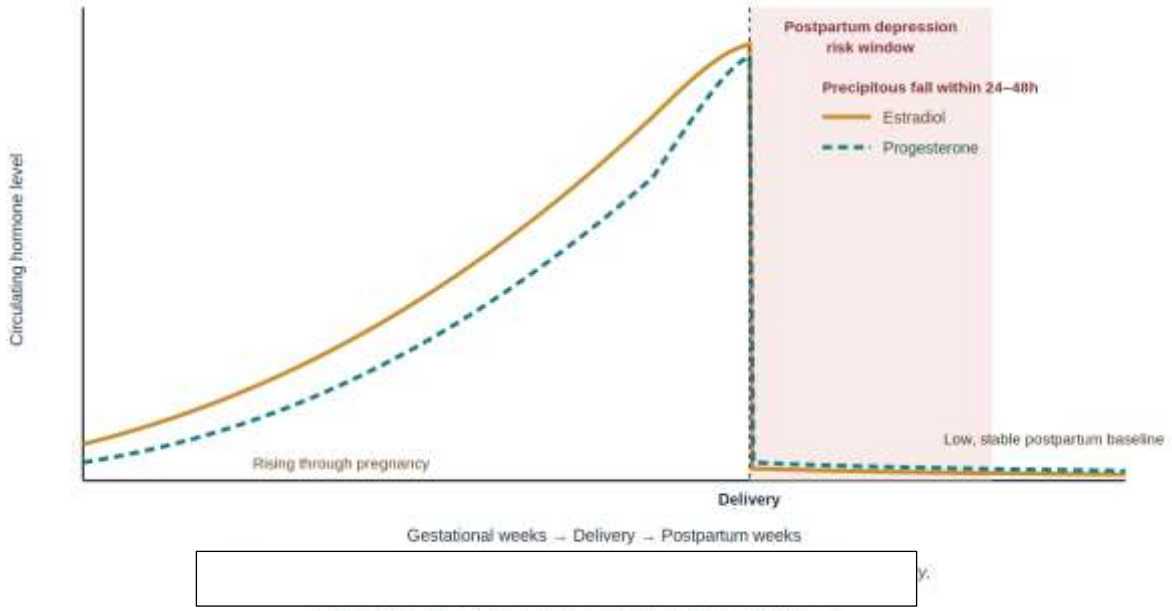

Figure 2. Estrogen and progesterone rise across pregnancy and fall precipitously after delivery, opening a biologically defined risk window for postpartum depression.

7. THE PERIMENOPAUSAL TRANSITION

7.1. STRAW staging and hormonal chaos

Perimenopause, formally staged using the Stages of Reproductive Aging Workshop (STRAW+10) criteria, typically begins in a woman's mid-to-late forties and lasts, on average, four to seven years before the final menstrual period (Harlow et al., 2012). Unlike the relatively predictable rise-and-fall rhythm of a normal menstrual cycle, perimenopause is characterised by increasingly erratic, unpredictable estradiol fluctuation, with levels that can spike well above typical premenopausal peaks before falling again, superimposed on a gradually declining ovarian reserve. This loss of predictability is itself clinically important: women can no longer easily anticipate their own hormonal state from the calendar, which may partly explain why perimenopausal mood symptoms often feel more disorienting and less "explainable" than familiar premenstrual patterns.

This unpredictability also creates a genuine diagnostic trap that deserves explicit mention: irritability, fatigue, weight change, low mood, and cognitive complaints during the perimenopausal years overlap substantially with thyroid dysfunction, iron deficiency, sleep apnoea, and primary depressive disorder unrelated to reproductive hormones at all. A woman in her late forties presenting with new fatigue and low mood deserves a basic evaluation for these alternative explanations before every symptom is attributed reflexively to "the change," just as, in the opposite direction, clinicians should be equally wary of chasing an exhaustive medical workup while ignoring a woman's own accurate observation that her symptoms are clearly tracking her increasingly erratic cycle.

7.2. The "window of vulnerability" for depression

Multiple community-based epidemiological studies converge on a strikingly consistent finding: women are somewhere between 1.5 and 3 times more likely to experience a first-onset or recurrent depressive episode during perimenopause compared with the years immediately before or well after it (Estrogen Receptor Beta and Mood, NIH protocol documentation, 2026 update; Freeman et al., 2004). This has become known in the literature as a biological "window of vulnerability," and it appears to be a genuinely distinct risk period rather than simply reflecting the ordinary life stresses of midlife, since the same epidemiological studies typically adjust for those confounding factors and the association persists.

7.3. Estradiol variability, not deficiency, drives the risk

It would be easy to assume perimenopausal depression simply reflects declining estrogen, in the same way that low thyroid hormone causes hypothyroid symptoms. The evidence tells a more interesting story. Multiple prospective studies converge on estradiol variability, the magnitude of week-to-week hormonal swings around a woman's own mean level, rather than the absolute level itself, as the stronger predictor of depressive symptom burden during the transition (Joffe et al., 2020; Gordon et al., 2019). One elegant pilot study directly measured this by tracking weekly estradiol alongside mood and found that larger week-to-week increases in estradiol, not simply low estradiol, predicted subsequent increases in sadness, hopelessness, guilt, and anxiety (Gordon et al., 2019). Freeman and colleagues, in an influential cohort study, further found that women were over nine times more likely to have had elevated FSH, and more than four times more likely to have had elevated LH, in the period preceding a depressive episode compared with earlier in their reproductive life, reinforcing that it is the turbulence of the transition itself, not a simple hormone deficiency state, that confers risk (Freeman et al., 2004).

7.4. Hormone therapy and mood

If variability rather than deficiency drives risk, it follows that stabilising hormone levels, rather than simply replacing them, should be therapeutically useful, and the trial evidence broadly supports this. A randomised clinical trial of transdermal estradiol combined with intermittent micronized progesterone meaningfully reduced the incidence of clinically significant depressive symptoms during the menopause transition compared with placebo (Gordon et al., 2018). Subsequent systematic reviews and meta-analyses of menopausal hormone therapy for perimenopausal depressive symptoms report a generally favourable, though not universal, effect, with regimens using micronized progesterone (as opposed to certain synthetic progestins) and steady, non-oral delivery routes showing particularly consistent mood benefit (Perimenopausal HT meta-analysis, 2026). This is a meaningfully different clinical picture from postmenopausal hormone therapy for vasomotor symptoms alone, and the two indications should not be conflated when counselling patients.

8. MENOPAUSE AND BEYOND

8.1. Vasomotor symptoms, sleep, and mood interplay

Menopause, defined retrospectively after twelve consecutive months without menstruation, is often discussed as though it were a single day rather than a physiological state that persists for the rest of a woman's life. Hormone levels stabilise, but at a low, estrogen-deficient baseline, and vasomotor symptoms, hot flashes and night sweats, affect a large majority of women during the transition and into early menopause. The relationship between these vasomotor symptoms and mood is genuinely bidirectional and mediated substantially through sleep: night sweats fragment sleep, fragmented sleep worsens next-day mood and irritability, and poor mood can itself worsen subjective sleep quality, a self-reinforcing cycle sometimes called the "domino hypothesis" of menopausal mood change (Freeman, 2015).

8.2. Cognitive changes ("brain fog")

Many women report word-finding difficulty, reduced concentration, and forgetfulness during the menopause transition, a cluster often described colloquially as "brain fog." Estrogen influences hippocampal and prefrontal cortex function directly, providing a plausible neurobiological basis for these complaints, and several longitudinal cohorts document objectively measurable, if generally modest and often reversible, changes in verbal memory and processing speed during the transition itself, typically improving again once hormone levels restabilise postmenopausally.

8.3. Long-term considerations

Beyond the acute transition, sustained estrogen deficiency after menopause carries broader implications for bone density, cardiovascular risk, and, per ongoing research, possibly long-term cognitive trajectory, though causal evidence in this last domain remains considerably less settled than for the acute mood and vasomotor effects discussed above. Decisions about menopausal hormone therapy for long-term use therefore require an individualised risk-benefit conversation that extends well beyond mood alone, and are appropriately made jointly between patient and clinician rather than dictated by any single symptom domain.

8.4. Premature and early menopause: a distinct risk category

Menopause occurring before age 40, termed premature ovarian insufficiency, and menopause occurring between 40 and 45, termed early menopause, deserve separate mention because they compress the entire hormonal transition described in this

section into a shorter, often more abrupt timeframe, frequently triggered by surgery, chemotherapy, or autoimmune ovarian failure rather than natural ageing. Women experiencing premature or early menopause face not only the acute mood and cognitive effects already discussed but also a substantially longer subsequent duration of estrogen deficiency exposure, with correspondingly greater long-term bone and cardiovascular implications, making the case for at least considering hormone therapy, absent specific contraindications, meaningfully stronger in this younger group than in women reaching menopause at the typical age.

9. A COMPARATIVE VIEW ACROSS THE REPRODUCTIVE LIFESPAN

Laid out side by side, the four windows discussed above share a common architecture even though they look quite different at the bedside: a genuine, measurable hormonal event; a plausible neuroendocrine mechanism linking that event to mood; and a subgroup of women whose brains respond to that event more intensely than the population average. Table 2 summarises this shared architecture across each life stage.

It is worth naming explicitly what varies across these four windows as well as what stays constant. The direction of hormonal change differs meaningfully: PMDD and postpartum depression both follow a hormone withdrawal pattern, whereas perimenopausal depression appears driven more by variability and unpredictability than by withdrawal in either direction, and menopausal mood change occurs against a backdrop of sustained low, stable hormones rather than an acute shift at all. Treatment implications follow this same logic rather than a single universal approach: withdrawal-pattern conditions respond well to therapies that either replace the withdrawn neurosteroid directly (brexanolone, zuranolone) or pre-empt the withdrawal through suppression (GnRH agonists, certain contraceptive regimens), whereas variability-pattern perimenopausal depression responds better to therapies that stabilise hormone levels into a steadier plateau. Recognising which pattern applies to a given patient, rather than applying a single hormone-therapy approach uniformly across all four life stages, is arguably the single most practically useful lesson this comparative view offers.

Life stage	Hormonal event	Approximate risk / prevalence	Leading mechanism	Evidence-based treatment
Late luteal phase (PMDD)	Post-ovulatory progesterone/allopregnanolone decline	3–8% (severe)	GABA-A sensitivity to ALLO withdrawal	SSRIs (continuous/luteal), hormonal suppression
Postpartum	Precipitous E2/P4 fall within 24–48h	11–17% globally (higher in LMICs)	Cellular stress-gene dysregulation; GABAergic imbalance	Brexanolone, zuranolone, SSRIs, psychotherapy
Perimenopause	Erratic, high-amplitude E2 variability	1.5–3x depression risk vs premenopause	Sensitivity to E2 variability, not deficiency	Transdermal E2 + micronized progesterone; SSRIs
Menopause	Low, stable, estrogen-deficient state	Variable; mediated via VMS and sleep	Sleep fragmentation ("domino" effect); direct E2-cognition links	HT for VMS; sleep and mood-targeted therapy

Table 2. Hormone-mood windows across the female reproductive lifespan.

Natural Resources for Human Health
eISSN: 2583-1194

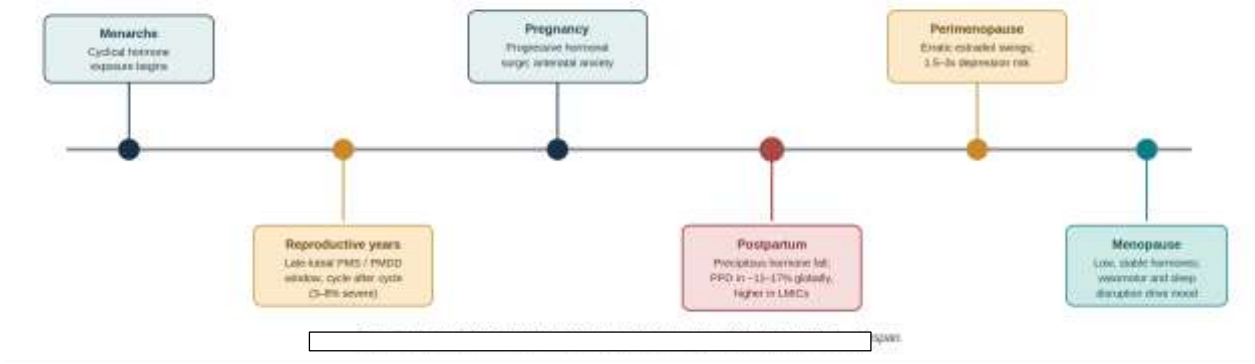

Figure 3. Windows of heightened hormone-mood sensitivity across the female reproductive lifespan.

10. CLINICAL ASSESSMENT: LEARNING TO LISTEN

10.1. Symptom tracking tools

Because timing, not symptom content alone, is what separates a hormone-sensitive mood pattern from a primary psychiatric disorder, prospective daily symptom tracking across at least two menstrual cycles is the diagnostic gold standard for PMS and PMDD, most formally captured by validated instruments such as the Daily Record of Severity of Problems (DRSP) (O'Brien et al., 2011). Retrospective recall is notoriously unreliable for this purpose; women (and their clinicians) consistently misjudge the true timing of their own symptoms when asked to remember rather than record them in real time. The same logic, if less formally codified, applies to postpartum and perimenopausal mood change: a simple daily or weekly log of mood, sleep, and, where relevant, menstrual bleeding pattern often reveals a pattern that neither patient nor clinician had previously recognised.

Cultural context shapes how readily women engage with this kind of tracking, and clinicians should not assume a uniform starting point across every patient population. In settings where menstruation itself remains a topic of social discomfort or even active taboo, simply asking a woman to keep a daily written record of her cycle and mood may require more explicit normalisation and reassurance of confidentiality than it would elsewhere. Framing symptom tracking as a practical diagnostic tool, no different in principle from a blood pressure diary or a glucose log, rather than as an invitation to dwell on emotional difficulty, can make this recommendation land considerably better across a wider range of cultural contexts.

10.2. Differentiating hormonal mood change from primary psychiatric illness

Not every low mood in a menstruating, pregnant, postpartum, or perimenopausal woman is hormonally patterned, and treating it as such by default risks missing a primary mood or anxiety disorder that requires its own independent treatment regardless of cycle phase. The clinically useful distinction is whether the woman has genuine symptom-free intervals: PMDD, by definition, resolves for at least several days each cycle, and typical PPD or perimenopausal depression, while less strictly time-bound, still generally responds to standard depression treatment protocols. Persistent, unremitting low mood with no clear symptom-free window, irrespective of reproductive stage, should prompt full psychiatric evaluation rather than being reflexively attributed to hormones.

10.3. Red flags requiring urgent care

Certain presentations require immediate escalation rather than watchful symptom tracking. These include any expression of suicidal ideation or self-harm at any reproductive life stage; the sudden onset of confusion, delusions, or hallucinations in the postpartum period, which may indicate postpartum psychosis; and severe, rapidly worsening mood symptoms that do not fit an expected hormonal timeline. In all of these situations, urgent professional psychiatric evaluation takes precedence over any amount of careful symptom charting, and clinicians should never let a hormone-sensitivity framework delay appropriate emergency care.

11. DISCUSSION: A CLINICIAN-SCIENTIST'S PERSPECTIVE

11.1. What the sensitivity model gets right

Having gone through this literature closely, my own view is that the hormone-sensitivity framework is one of the more genuinely useful reframes to emerge in reproductive medicine in the past thirty years, and it deserves wider circulation well beyond specialist psychiatric literature. It replaces a moralising, faintly dismissive question, "why are you so emotional?", with a testable clinical one, "is there a pattern to when you feel this way?" That shift matters not just rhetorically but practically: it points directly toward a diagnostic method, prospective symptom tracking, and toward specific, mechanistically targeted treatments, luteal-phase SSRIs, neurosteroid therapeutics, hormone stabilisation, rather than a vague prescription to simply cope better.

11.2. Where caution is genuinely needed

That said, I want to push back gently on one direction this framework could be taken too far. There is a real risk, particularly as this science reaches wider public audiences, of swinging from decades of dismissing every female emotion as psychological to now attributing every female emotion to hormones instead. Both extremes fail women, just in opposite directions. Not every argument is PMS. Not every anxious thought during pregnancy is a hormonal inevitability. Not every episode of sadness after childbirth needs, or benefits from, a hormonal explanation, and plenty of postpartum depression is driven substantially by sleep deprivation, relationship strain, financial stress, and inadequate social support, factors that a neurosteroid, however well-targeted, cannot fix on its own. The honest clinical position is neither "it's just hormones" nor "it's not hormones at all," but rather a disciplined habit of asking, case by case, how much of this particular woman's particular experience the biology actually explains.

I would add one further caution from my own reading of this evidence base: much of the foundational mechanistic work described in this review, the ovarian suppression paradigm, the ESC/E(Z) cellular studies, the neurosteroid pharmacology, comes from a relatively small number of research groups working with modest sample sizes, as is common in specialised experimental psychiatry. The findings have been replicated meaningfully across studies and across different life stages, which strengthens confidence in the underlying sensitivity model considerably, but the field would benefit from larger, more demographically diverse cohorts, particularly outside North America and Western Europe, before the model is treated as fully settled science rather than a well-supported and rapidly maturing one.

11.3. The stigma paradox: from "hysterical" to "hypersensitive"

There is also a subtler risk worth naming directly. Historically, women were dismissed as "too sensitive" as an insult; there is a genuine danger that a hormone-sensitivity model, however scientifically accurate, could be quietly repackaged into the same old insult wearing a lab coat, this time framed as "your biology makes you more sensitive" rather than "you are being dramatic." The distinction that has to be actively protected in how this science is communicated is that sensitivity, in this context, is a measurable, mechanistic, and in no way pejorative biological trait, akin to drug sensitivity or allergic sensitivity, not a euphemism for excess emotionality. Getting that framing right, in clinics and in public communication alike, is not a minor semantic detail; it is the entire point of moving away from the language of hysteria in the first place.

12. IMPLICATIONS FOR CLINICAL PRACTICE AND PUBLIC HEALTH

12.1. Medical education

Reproductive psychiatry remains a strikingly small component of most undergraduate medical curricula relative to how many women it affects across a working clinical career. Given that essentially every practising physician, regardless of specialty, will encounter menstruating, pregnant, postpartum, perimenopausal, and menopausal patients, basic competency in hormone-mood assessment, including how and when to use structured symptom tracking, arguably belongs in general medical training rather than being confined to psychiatry and gynaecology subspecialty rotations alone.

12.2. Workplace and social policy

Beyond the clinic, this evidence base has real implications for workplace policy, particularly around menstrual and menopause-related accommodation, and for perinatal mental health screening programmes, which remain inconsistently implemented even in well-resourced health systems and are frequently absent altogether in lower-resource settings where postpartum depression prevalence is often highest. Universal postpartum depression screening using validated tools such as the Edinburgh Postnatal

Depression Scale, paired with a genuine referral pathway rather than screening alone, represents one of the more cost-effective public health interventions available in maternal mental health, precisely because the underlying biology creates such a predictable, time-limited window in which to intervene.

12.3. Global disparities in perinatal and menopausal care

The higher postpartum depression prevalence documented in low- and middle-income countries almost certainly reflects a combination of biological universality and unequal social and healthcare context rather than any difference in underlying neuroendocrine vulnerability. Neurosteroid therapeutics such as brexanolone and zuranolone, for all their mechanistic elegance, remain expensive and, in the case of brexanolone, logistically demanding, meaning the populations with the highest measured burden of postpartum depression are frequently the least likely to access its most targeted treatments, a disparity that deserves far more attention in global maternal health policy than it currently receives.

13. FUTURE DIRECTIONS

Several research priorities follow directly from the evidence reviewed here. First, extending the cellular and genetic sensitivity paradigm established for PMDD and postpartum depression to perimenopausal depression, where a comparably direct mechanistic study has not yet, to this reviewer's knowledge, been published, would meaningfully strengthen the unified framework this review proposes. Second, developing accessible, affordable neurosteroid or neurosteroid-adjacent therapeutics suitable for lower-resource health systems would directly address the global equity gap described above. Third, prospective, cycle-tracking-based research using increasingly ubiquitous smartphone and wearable technology could finally generate population-scale data on how common genuine hormone-sensitive mood patterns are, moving the field beyond clinic-based samples that likely both underrepresent mild cases and over represent severe, treatment-seeking ones. Finally, and perhaps most importantly from a communication standpoint, dedicated research into how hormone-sensitivity science is understood, and potentially misused or over-applied, by the public would help ensure this genuinely useful biological reframe does not calcify into a new, subtler version of the very dismissiveness it was meant to correct.

14. CONCLUSION

A woman describing ten days a month in which she feels unlike herself is not, in most cases, describing instability of character. She is describing a nervous system that responds with unusual intensity to a hormonal rhythm every ovulating woman experiences, whether or not she notices it. The same underlying principle, differential brain and cellular sensitivity to normal, not abnormal, hormonal change, reappears with striking consistency across the menstrual cycle, the postpartum period, and the perimenopausal transition, and it has already produced real diagnostic clarity and real, mechanistically targeted medicines rather than remaining an abstract idea. The task now is to carry that clarity into ordinary clinical practice and everyday conversation without swinging into the opposite error of explaining away every difficult female emotion as hormonal. The woman is not broken. Her biology is not a flaw to be managed into silence. She is, in a very literal, measurable, and increasingly treatable sense, sensitive — and learning to listen to what that sensitivity is actually saying, carefully and without either dismissing or over-medicalising it, is the real clinical work ahead.

15.ETHICAL CLEARANCE: The article being a review article is not prudent to get clearance from ethical committee.

16.CONFLICT OF INTEREST: The author declares no Conflict of Interest with any person or organization.

17.FUNDING: Self-funding.

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