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HORMONAL FLUCTUATIONS AND PULSATILLA VARIABILITY: AN INTEGRATIVE HYPOTHESIS

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ABSTRACT

Hormonal fluctuations represent an essential component of female reproductive physiology and are particularly prominent during the menstrual cycle and reproductive transitions such as puberty, pregnancy, postpartum period, perimenopause and menopause. Ovarian steroid hormones, principally estradiol and progesterone, exert effects beyond reproductive tissues and interact with neural circuits involved in mood, cognition, sleep, appetite, stress responsiveness and emotional processing. Increasing evidence indicates that clinically relevant symptoms in susceptible individuals may depend not simply upon absolute hormone concentrations but upon individual sensitivity to physiological hormonal fluctuations^[1,2]

Pulsatilla occupies a distinctive position in classical homoeopathic Materia medica because of its characteristic variability and its prominent association with female reproductive symptoms. Classical sources describe changeable mental states, easy weeping, mildness and yielding behaviour, desire for consolation, shifting physical symptoms, delayed or scanty menstruation, intermittent menstrual flow, leukorrheal symptoms and manifestations associated with pregnancy and lactation^[5,7]

Modern pharmacognostic investigations of Pulsatilla species have identified several bioactive constituents, particularly triterpenoid saponins. Research involving *Pulsatilla nigricans* has characterized compounds including anemoside B4, anemoside A3 and other saponins, with

experimental evidence for anti-inflammatory, immunomodulatory, antioxidant and other pharmacological activities^[9,11]

This article proposes an integrative hypothesis in which the classical concept of Pulsatilla variability is examined alongside the modern concept of neuroendocrine sensitivity to hormonal fluctuations. The hypothesis does not assert that hormonal fluctuations cause the Pulsatilla symptom complex, nor that Pulsatilla regulates reproductive hormones. Instead, it proposes that the temporal variability, reproductive associations and affective characteristics described in Pulsatilla may constitute a clinically observable phenotype worthy of prospective investigation using menstrual cycle tracking, validated symptom instruments and endocrine biomarkers.

KEYWORDS: Pulsatilla; hormonal fluctuations; neuroendocrinology; hormone sensitivity; reproductive physiology; integrative hypothesis.

INTRODUCTION

Female reproductive physiology is characterized by rhythmic changes in hypothalamic, pituitary and ovarian activity. The hypothalamic-pituitary-ovarian axis regulates follicular development, ovulation and corpus luteum function through coordinated secretion of gonadotropin-releasing hormone, follicle-stimulating hormone and luteinizing hormone, resulting in cyclical variation in ovarian steroid hormones. Estradiol predominates in the follicular phase, whereas progesterone rises substantially after ovulation during the luteal phase^[1,2]

The biological actions of reproductive hormones extend beyond the reproductive tract. Estrogen and progesterone interact with the central nervous system and may influence neurotransmission, neural plasticity, emotional processing, cognition, sleep, appetite, stress responses and thermoregulation^[2,3] Consequently, physiological hormonal fluctuations may be accompanied by changes in symptoms and behavior in some individuals.

However, hormonal fluctuation should not be equated with disease. Most menstruating individuals do not develop clinically significant affective symptoms as a consequence of normal reproductive hormone changes. Contemporary research increasingly emphasizes the concept of hormone sensitivity, whereby a subgroup of individuals demonstrates increased susceptibility to the effects of changing ovarian steroid exposure^(3,4)

This distinction is particularly relevant in premenstrual disorders. Evidence from premenstrual dysphoric disorder research indicates that ovarian steroid concentrations may be

within the physiological range while symptoms arise because of altered central sensitivity to hormonal changes or their neuroactive metabolites^(3,4)

Within classical homoeopathic literature, Pulsatilla is repeatedly characterized by variability and changeability. Hering describes rapidly changing mental and physical states, easy weeping, mildness, desire for consolation and alternating manifestations.^[5] Kent emphasizes emotional sensitivity, mildness, yielding behaviour and changeability.^[6] Clarke describes numerous reproductive manifestations, particularly delayed and variable menstruation.^[7]

The female reproductive sphere occupies a prominent position in the traditional Pulsatilla picture. Classical sources describe delayed, scanty or intermittent menstruation, leucorrhoea, pregnancy-related complaints and disturbances associated with lactation^[5,6]

The apparent conceptual overlap between two observations that physiological variability in reproductive hormones and variability within the Pulsatilla symptom complex provides the rationale for the present hypothesis.

NEUROENDOCRINE FRAMEWORK

Hypothalamic-Pituitary-Ovarian Axis

The hypothalamic-pituitary-ovarian (HPO) axis is the principal neuroendocrine regulatory system governing female reproductive function. Hypothalamic neurons release gonadotropin-releasing hormone (GnRH) in a pulsatile manner. GnRH stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These gonadotropins regulate ovarian follicular development, steroidogenesis and ovulation^[1,2]

During the follicular phase, developing ovarian follicles produce increasing concentrations of estradiol. Sustained high estradiol concentrations contribute to the positive feedback responsible for the preovulatory LH surge. Following ovulation, the corpus luteum produces progesterone together with estradiol. In the absence of pregnancy, regression of the corpus luteum leads to declining progesterone and estradiol concentrations, contributing to endometrial shedding and menstruation.^[1,2]

Estradiol and the Central Nervous System

Estrogen receptors are distributed throughout several brain regions involved in emotional and cognitive regulation. Estradiol can influence serotonergic, dopaminergic, glutamatergic and GABAergic neurotransmission as well as neural plasticity and stress-responsive systems^[2,4]

Changes in estrogen exposure may therefore influence:

- Mood
- Emotional processing
- Cognition
- Appetite
- Sleep
- Sensory processing
- Stress responsiveness

The effects are not uniform among individuals, emphasizing the importance of biological susceptibility and contextual factors.^[3,4]

Progesterone and Neuroactive Steroids

Progesterone also has important neurobiological effects. Its metabolites include neuroactive steroids such as allopregnanolone, which modulate GABA-A receptor activity.^[3,4]

Changes in neuroactive steroid exposure are:

- Anxiety
- Irritability
- Emotional reactivity
- Sleep
- Stress sensitivity
- Premenstrual symptoms

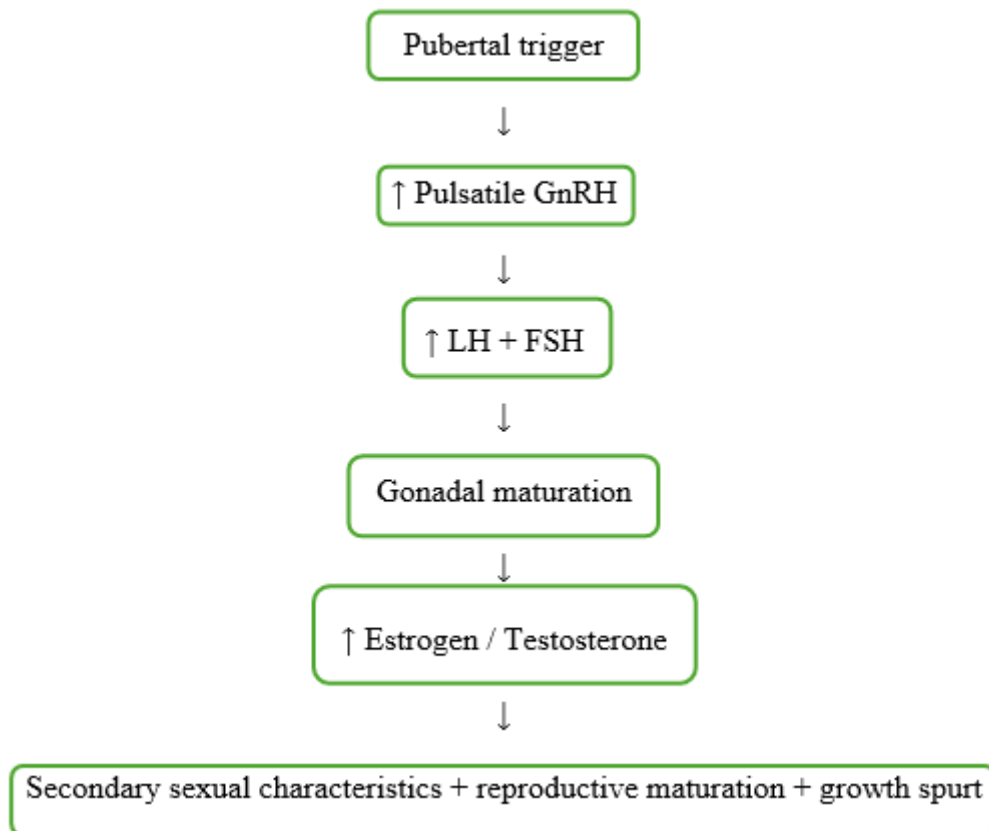
Importantly, current models of premenstrual disorders do not simply attribute symptoms to excessive or deficient progesterone. Instead, differential sensitivity to normal cyclical changes in ovarian steroids and their metabolites is increasingly emphasized^[3,4]. This concept of sensitivity to fluctuation forms a central component of the present hypothesis.

HORMONAL FLUCTUATIONS THROUGHOUT THE REPRODUCTIVE LIFE CYCLE

Puberty

Puberty represents the reactivation and maturation of the HPO axis. Increasing gonadal steroid secretion accompanies changes in reproductive development, body composition,

sleep, emotional regulation and neurodevelopment. The transition is therefore a period of substantial neuroendocrine change. (Flowchart 1)



Flowchart 1: Hormonal Cycle During Puberty.

Menstrual Cycle

The menstrual cycle can broadly be divided into:

1. Menstrual phase
2. Follicular phase
3. Ovulatory phase
4. Luteal phase

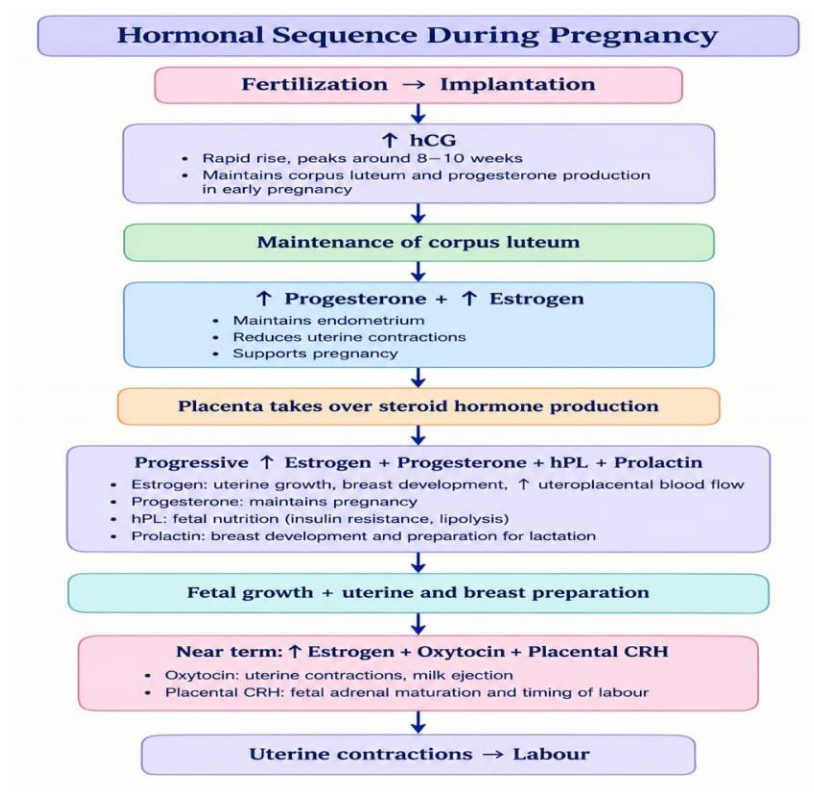
Estradiol and progesterone undergo characteristic changes throughout these phases ^[1,2]. The late luteal decline in ovarian steroids immediately precedes menstruation and has relevance to premenstrual symptomatology in hormone-sensitive individuals ^[3,4] (fig 1).

Hormone	Menstrual Phase (Days 1–5)	Follicular Phase (Days 1–13)	Ovulation (Around Day 14)	Luteal Phase (Days 15–28)
FSH	↑ Begins to rise	↑ Initially, then ↓	Small surge	↓ Low
LH	Low	Gradual ↑	Marked LH surge	↓ Low
Estrogen	↓ Low	Progressively ↑	Peak	Moderate ↑
Progesterone	↓ Low	Low	Low	Marked ↑
Inhibin B	Low–moderate	↑	↓	Low
Inhibin A	Low	Low	↑	↑
Main ovarian event	Follicles begin developing	Dominant follicle develops	Ovulation	Corpus luteum formation
Endometrial changes	Shedding	Proliferation	Transition	Secretory phase

Figure 1: Hormonal Variations Through Menstrual Cycle.

Pregnancy

Pregnancy produces profound changes in reproductive hormones. Estrogen and progesterone concentrations increase considerably, while placental and hypothalamic-pituitary adaptations alter multiple endocrine systems. (Flowchart 2)



Flowchart 2: Hormonal Sequence During Pregnancy.

These changes are accompanied by alterations in:

- Mood
- Sleep
- Appetite
- Gastrointestinal function
- Thermoregulation
- Breast physiology
- Reproductive tract function

Postpartum Period

After delivery, the abrupt withdrawal of placental progesterone and estrogen is accompanied by major neuroendocrine changes. Prolactin and oxytocin become particularly important in lactation and maternal behavior. The postpartum period is also a period of increased vulnerability to mood disturbances in susceptible individuals. (Table 1)

Primary Hormonal Shifts

- **Oestrogen & Progesterone:** Peak to extremely high levels during pregnancy, then plummet to near-zero within 24 to 48 hours after placental delivery.
- **Prolactin:** Surges immediately after birth to stimulate breast milk production. If breastfeeding, prolactin stays elevated; if not, it gradually returns to baseline over a few weeks.
- **Oxytocin:** Known as the "love hormone," it spikes during labor and continues to release in bursts during breastfeeding or skin-to-skin contact to facilitate milk letdown and uterine contractions (involution).
- **Cortisol & Thyroid Hormones:** Cortisol (stress hormone) spikes during labor and drops sharply after, while thyroid hormone levels fluctuate as the body's metabolism readjusts, sometimes leading to postpartum thyroiditis.

Table 1: Hormonal correlation with common manifestations during postpartum.

Symptom Category	Associated Hormonal Cause	Common Manifestations
Mood & Emotion	Drop in Oestrogen & Progesterone	"Baby blues" (days 3–10), mood swings, crying spells, vulnerability to Postpartum Depression (PPD) or Anxiety (PPA).
Body Temperature	Drop in Oestrogen	Night sweats, hot flashes, intense chills in the first few weeks.
Hair & Skin	Oestrogen normalization	Postpartum hair shedding (telogen effluvium, peaking around 3–4 months), skin breakouts, or dryness.
Energy & Metabolism	Thyroid & Cortisol shifts	Fatigue, joint pain, sluggishness, or postpartum thyroid issues (hyper- or hypothyroidism).
Sexual Health	Low Oestrogen + High Prolactin	Vaginal dryness, lowered libido, and temporary natural suppression of ovulation (lactational amenorrhea).

Perimenopause and Menopause

Perimenopause is characterized by increasing variability in ovarian function and reproductive hormone concentrations before the eventual decline in ovarian activity.

- Ovarian follicular reserve gradually declines.
- Inhibin B decreases, causing FSH to rise.
- Estrogen levels become highly fluctuating and eventually decline.
- Ovulation becomes irregular, leading to reduced progesterone production.
- Menstrual cycles become irregular, with changes in flow and duration.

Hormonal variability during this period may be associated with:

- Vasomotor symptoms – hot flashes, night sweats, chills, palpitation, anxiety.
- Sleep disturbance - insomnia, nightmare awakening, early morning awakening, reduced sleep quality
- Mood symptoms – irritability, emotional sensitivity, mood swings, poor concentration, overwhelming
- Menstrual irregularity – irregular cycle, heavy menstrual bleeding, scanty skipped anovulatory cycle.

Menopause

- Ovarian follicular activity ceases, resulting in markedly decreased estrogen and progesterone.
- Loss of negative feedback causes markedly increased FSH and increased LH.
- Ovulation and menstruation permanently cease.
- Low estrogen contributes to hot flushes, vaginal dryness, sleep disturbances and bone loss

PULSATILLA IN HOMOEOPATHIC MATERIA MEDICA

Botanical Identity

- **Kingdom:** Plantae
- **Family:** *Ranunculaceae* (Buttercup family)
- **Subfamily:** *Ranunculoideae*
- **Genus:** *Pulsatilla* Mill.
- **Species:** *Pulsatilla pratensis* (L.) Mill.

Constitutional Picture of Pulsatilla

Table 2: General Constitutional Picture: a comparative aspect.

Feature Domain /	James Tyler Kent (Lectures on Homeopathic Materia Medica)	Constantine Hering (The Guiding Symptoms of Our Materia Medica)
Mental Picture	Mild, Yielding, & Dependent: Weeps easily while telling symptoms, seeks sympathy, timid, irresolute, and strongly ameliorated by consolation.	Hypochondriac moroseness; out of sorts with everything. Gloomy, melancholic mood. gentle, yielding disposition. Silent mood; inclined to silent grief with submissiveness. tears very easily
Thermal Modalities	Marked Warm-Bloodedness: Strongly aggravated by heat and warm rooms; strongly ameliorated by cool, fresh, open air.	Specific Local Modalities: Heat of stove: Hot rooms and cold vaults (ailment factor) Emphasizes local temperature changes (e.g., relief from cold applications to inflamed joints, aggravation from cold drinks).
Central Pathological Theme	Erraticism & Changeability: "No two stools, no two chills are alike." Rapidly wandering	Etiology & Specific Trigger Factors: Triggers include eating pork or rich/fatty foods, ice cream, getting feet wet, or suppressed

Feature Domain /	James Tyler Kent (Lectures on Homeopathic Materia Medica)	Constantine Hering (The Guiding Symptoms of Our Materia Medica)
	pains; sluggish venous stasis.	menses/lochia.
Thirst & Secretions	General Thirstlessness: Complete absence of thirst, even with a dry mouth or fever; discharges are uniformly thick, bland, and yellow green.	Detailed Discharge Attributes: Categorizes secretions by specific anatomical sites (e.g., thick, dark, intermittent menstrual flow; catarrhal otitis media with green discharge).
Gastrointestinal Picture	General aversion to fatty foods linked to a sluggish, timid constitution.	Specific gastric sensations, such as a "stone in the stomach" an hour after eating, bitter eructation, and slow digestion from butter or pastry.
Respiratory Pattern	Broadly notes the shifting nature of coughs and chest congestion in cold versus warm environments.	Keynote distinction: Dry, paroxysmal cough at night (forcing the patient to sit up), changing to a loose, productive cough in the morning .
Pain Characteristics	Drawing, wandering pains that shift rapidly from one part of the body to another.	Pains that slowly increase in intensity to a peak and disappear with a sudden snap , accompanied by chilliness without thirst.

Changeability of symptoms:

Changeability is one of the most recognizable characteristics associated with Pulsatilla.

Classical descriptions include:

- Rapid changes in mood
- Alternating crying and relative cheerfulness
- Changing location of symptoms
- Variable intensity of complaints
- Alternating symptoms
- Inconsistent or shifting physical manifestation

PULSATILLA IN FEMALE REPRODUCTIVE SYSTEM:

Menstrual Symptoms

Classical Materia Medica describes Pulsatilla in association with:

- Indicated for delayed first menses in young girls at puberty,

- Suppressed menses from getting the feet wet, from getting cold, with nausea and vomiting
- Delayed menstruation
- Scanty menstruation
- Intermittent flow
- Variable menstrual characteristics
- Dark or clotted menstrual blood
- Changes in menstrual flow – thick, dark and clotted or thin, watery
- Menstrual symptoms accompanied by emotional changes.
- Menstrual colic with great restlessness
- Habitual loose of bowels with metrorrhagia

Leucorrhea

Classical sources describe several types of leucorrhea discharge including ^[5,7].

- painless, thick mucus, color of milk, creamy
- Acrid, thin with burning and pruritus
- Associated with swelling of pudenda, backache and hysterical symptoms

Pregnancy and Lactation

Pulsatilla Materia Medica includes several pregnancy-related symptoms, including uterine and breast complaints. ^[5-8]

- Threatened abortion, flow ceases, and then returns with double force
- Action of womb is insufficient for expulsion
- Suppression or very scanty supply of milk
- Swelling of breast
- Morning sickness and vomiting of sour mucus
- Fluor albus and false labor pain
- Milk suddenly suppressed, lochia become milky white
- Malposition of fetus
- postpartum secondary hemorrhage from retained placenta
- mild tearful women who have but little milk- thin and watery, the true milk globule almost entirely absent.

PHYTOCHEMISTRY AND PHARMACOLOGY OF PULSATILLA

Phytoconstituents of pulsatilla have an effective role on sedative, analgesic, anti-inflammatory, antioxidant activity and other effects. [21]

The main phytochemical constituents discovered in pulsatilla are [9,10]

- Triterpenoid saponins- major active component
- Ranunculin and other toxins
- Flavonoids – astragalin
- Phenolic and Phenyl propionic acids
- Others- lignans, coumarins, steroids, volatile oils and tannins.

Triterpenoid saponins

- Anemoside B4 - an abundant triterpenoid saponin investigated its effects on inflammatory signaling including pathways involving NF- κ B and inflammatory cytokines
- anemoside A3
- Pulsatilla saponin D
- other triterpenoid saponins

Pharmacological Activities

1. Anti-inflammatory activity – the saponins AB4 causes regulation of immune function by inhibiting TNF α , IL1 β and IL6 and inhibiting transcription signaling pathways, thereby nuclear factor kappa B is enhanced [11]
2. Antioxidant Effects - The antioxidant activity of saponins involves different mechanisms P. nigricans extract can specifically increase superoxide and markedly increase mitochondria MnSOD activity in liver tissue at the same time, which may prevent possible infections and superoxide-mediated toxicity [9]
3. Antimicrobial effects-highly effective against gram-positive, gram-negative bacteria, *Trichomonas vaginalis*, *Schistosoma japonicum*, *Toxoplasma gondii*, *Euphorbium resinifera* [9]
4. Immunomodulatory activity – AB4 might effectively regulate immune responses via regulating the production of certain cytokines Th2 Cytokines, Th1 cytokines, IL2 ,IL4, IL10.[9]
5. The organ protective activity -AB4 showed detoxicating effect against cisplatin caused body weight loss and kidney injury without reducing anti-cancer activity. It increases adenine

content and promotes its excretion, thereby promoting glomerular matrix from adenine injury. [9]

6. Anticancer activity^[9]

- effects on apoptosis
- inhibiting angiogenesis and cellular proliferation
- regulating autophagy and cell cycle

COMPARATIVE ANALYSIS: PULSATILLA SYMPTOMS AND HORMONAL CORRELATES

Table 3: Conceptual comparison of Pulsatilla variability with neuroendocrine phenomena.

Pulsatilla characteristics	Classical source	Potential modern physiological correlate	Evidence status
Rapid Emotional changeability	Hering, Kent	Hormone-sensitive affective processing	Hypothesis
Easy, frequent weeping	Hering, Kent	Mood regulation and neurosteroid sensitivity	Hypothesis
Desire for consolation	Hering, Kent	Attachment/affective regulation	Hypothesis
Delayed menses	Hering, Clarke	Altered menstrual-cycle physiology	Association only
Scanty/intermittent flow	Hering, Clarke	Menstrual/endometrial variability	Association only
Variable uterine symptoms	Hering, Clarke	Major reproductive endocrine transition	Biological overlap
Lactation complaints	Hering, Clarke	Prolactin/oxytocin physiology	Biological overlap
Variable appetite	Materia medica	Hormonal effects on appetite pathways	Hypothesis
Chilly but with episodes of heat-Thermal variability	Materia medica	Estrogen-associated thermoregulation	Hypothesis
Shifting symptoms	Hering, Kent	Dynamic neurophysiological symptom processing	Hypothesis

1. Emotional variability^(5,6)

- Easy weeping
- Rapid emotional changes
- Mildness
- Sensitivity
- Desire for consolation
- Alternating emotional states

Modern Endocrine Context

Fluctuations in ovarian steroid hormones particularly estradiol and progesterone-derived neurosteroids such as allopregnanolone, can influence emotional regulation through serotonergic, GABAergic and hypothalamic–pituitary–adrenal (HPA) axis mechanisms ⁽¹²⁾. Importantly, affective symptoms may reflect individual sensitivity to hormonal fluctuations rather than simply abnormal hormone concentrations. Social buffering leads to oxytocin activation by physical proximity and verbal reassurance and leads to activation of reward loop, cortisol counterbalance. This suppresses the release of cortisol and eases their emotions. ⁽¹³⁾

Hypothesis

The classical description of Pulsatilla includes a marked tendency to weep readily, including while speaking and in response to both pleasant and unpleasant experiences, together with emotional variability and changeability. ⁽⁵⁾ These phenomenological features may be hypothesized as a possible correlate of increased neuroendocrine sensitivity and altered emotional regulation during hormonally dynamic states. Contemporary research indicates that affective responses to reproductive hormones may depend substantially on individual sensitivity to fluctuations in ovarian steroid hormones, rather than simply on absolute hormone concentrations. ⁽¹²⁾

2. Thermal variability

Pulsatilla with marked alternation between chilliness and heat, intolerance of external warmth, hot flushes, cold hands/feet, localized or shifting sensations of heat and cold, chilliness even in warm weather, desire for open air and variable thermal states. ^(5,6)

Modern Endocrine Context

Estradiol and progesterone exert important effects on thermoregulation. Estradiol generally facilitates heat dissipation, whereas progesterone has a thermogenic effect and contributes to an elevation of core body temperature. Across the menstrual cycle, core temperature typically increases by approximately 0.3–0.7°C during the post-ovulatory luteal phase, when progesterone concentrations are elevated. ^(14,15) Reproductive hormones also influence central and autonomic mechanisms involved in skin blood flow and sweating. ^(14,15) During the menopausal transition, changing or declining estrogen exposure can disrupt thermoregulatory control and contribute to vasomotor symptoms such as hot flushes. ^(16,17)

Hypothesis

The characteristic alternating chilliness, heat intolerance and flushing described in Pulsatilla may phenomenologically resemble heightened sensitivity to dynamic reproductive-hormone-mediated thermoregulatory changes, particularly fluctuations in estrogen and progesterone and their effects on hypothalamic and autonomic temperature-control mechanisms. ⁽⁵⁾

3.Appetite and digestive variability

Pulsatilla with variable appetite—loss of appetite, hunger without knowing what desired, poor relish for food is, aversion to fatty/rich foods, nausea or vomiting after eating, bloating and flatulence after meals, and digestive disturbance from rich/fatty foods. ^(5,6)

Modern Endocrine Context

The bidirectional relationship between reproductive hormones and the gut–brain axis is increasingly recognized. Fluctuations in ovarian hormones, particularly estradiol and progesterone, can influence central appetite-regulatory pathways as well as gastrointestinal motility and visceral sensitivity. Ovarian steroids also interact with metabolic and gastrointestinal signaling systems involved in energy balance, including ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), thereby potentially modifying hunger, satiety and postprandial responses.^(18,19) Sex-steroid fluctuations across the menstrual cycle have also been associated with changes in gastrointestinal transit and visceral sensitivity, supporting an interaction between reproductive endocrine signaling and gut–brain pathways.⁽²⁰⁾

Hypothesis

The characteristic variability of appetite and digestion described in Pulsatilla may phenomenologically reflect increased sensitivity to HPO-axis-associated hormonal fluctuations and altered gut–brain neuroendocrine signaling. In this proposed model, gastrointestinal peptides, autonomic regulation and metabolic signals may dynamically influence hunger, satiety, gastric motility and postprandial symptoms, with reciprocal effects between gastrointestinal and neuroendocrine regulation. ⁽²⁰⁾

4.Delayed menses and variable uterine symptoms

Menses too late, scanty, slimy, irregular but more active during the day and stops on lying down. The labor like uterine pains shift, stop and return erratically. ^(5,6)

Modern Endocrine Context

Stress-related activation of the hypothalamic–pituitary–adrenal (HPA) axis can interact with the hypothalamic–pituitary–ovarian (HPO) axis. In functional hypothalamic amenorrhea, psychological or physiological stress is associated with altered GnRH pulsatility, reduced gonadotropin secretion and impaired ovarian function, resulting in delayed or absent menstruation. Increased HPA-axis activity and cortisol signaling are among the neuroendocrine alterations associated with this reproductive suppression. ^(21,22)

Prostaglandins are important mediators of menstruation and uterine contractility. In particular, PGF_{2α} promotes myometrial contraction and vasoconstriction, while excessive or dysregulated prostaglandin activity can produce stronger, more frequent and dysrhythmic uterine contractions associated with menstrual cramping. ^(23,24)

Hypothesis

Functional hypothalamic suppressive-pulse hypothesis: Under conditions of significant psychological or physiological stress, increased HPA-axis activity and cortisol signaling may interfere with the normal pulsatile regulation of GnRH, thereby disrupting HPO-axis function and potentially contributing to delayed or irregular menstruation. ^(21,22)

Prostaglandin–progesterone synchrony hypothesis: During an irregular or delayed menstrual cycle, altered ovarian-steroid dynamics, particularly changes associated with progesterone withdrawal, may modify endometrial prostaglandin production. Variation in prostaglandin activity could consequently influence the intensity, frequency and coordination of myometrial contractions, providing a possible physiological framework for the intermittent, shifting or recurrent uterine pains described in the Pulsatilla symptom picture. ^(23,24)

5.Shifting symptoms

Symptoms ever changing; no two chills, no two stools no two attacks alike; very well one hour, very miserable the next; apparently contradictory.

Pains: drawing, tearing, erratic, rapidly shifting from one part to another; are accompanied by constant chilliness; the more severe the pain, the more severe the chill. ⁽²⁸⁾

Modern Endocrine Context

The HPA axis and female reproductive system are closely interconnected, with glucocorticoids and stress-related signaling capable of influencing reproductive neuroendocrine function, while ovarian steroids can in turn modulate stress and pain pathways ⁽²⁵⁾. Estradiol and progesterone also influence central and peripheral nociceptive

mechanisms, and fluctuations in ovarian hormones have been associated with changes in pain sensitivity across the menstrual cycle. ⁽²⁶⁾ Autonomic and thermoregulatory responses are similarly influenced by reproductive hormones, with changes in estradiol particularly affecting vasomotor and thermoregulatory mechanisms. ⁽²⁷⁾

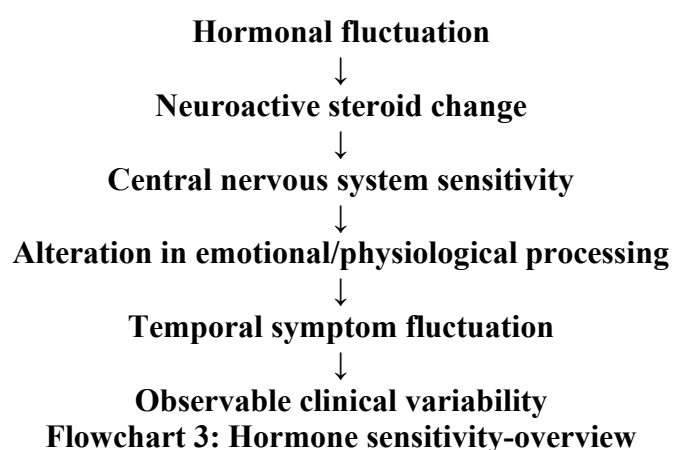
Hypothesis

HPA–HPO axis desynchronization

The HPA–HPO axis desynchronization hypothesis proposes that altered coordination between stress-related cortisol signaling and ovarian steroid fluctuations may contribute to variability in pain perception and autonomic symptoms. Rather than assuming a predictable sudden fall in estradiol or rise in cortisol at a particular time of day, the hypothesis proposes that individual differences in neuroendocrine sensitivity and temporal hormone dynamics could produce intermittent changes in nociceptive processing, vascular regulation and autonomic function. Thus, the characteristics of rapidly shifting or wandering pains described in Pulsatilla may phenomenologically resemble a state of variable neuroendocrine and autonomic regulation. ^(26,27) The proposed daytime-to-evening pattern, relative activity and reduced pain followed by later emergence of pain, vasomotor symptoms or emotional changes.

HORMONE SENSITIVITY AS A POSSIBLE EXPLANATORY FRAMEWORK

Contemporary research distinguishes between hormone concentration and hormone sensitivity. A person may have reproductive hormone concentrations within the normal physiological range but experience substantial symptoms during hormonal transitions because of increased biological sensitivity ^(3,4). This concept provides a potentially useful framework for examining the classical Pulsatilla emphasis on variability. (Flowchart 3)



PROPOSED INTEGRATIVE HYPOTHESIS

Proposed Integrative Hypothesis

The central hypothesis of this study is that the characteristic variability of the Pulsatilla symptom complex—including fluctuations in emotional state, easy weeping, consolation-seeking behavior, changing physical symptoms and variable menstrual and reproductive manifestations—may represent a clinically recognizable phenomenological pattern that can be investigated in relation to individual neuroendocrine sensitivity to physiological hormonal fluctuations, particularly fluctuations in ovarian steroid hormones.

The proposed framework consists of three sequential levels of evidence:

Level 1 – Classical clinical observation:

The traditional Materia medica describes a characteristic pattern of emotional variability, easy weeping, desire for consolation, rapidly changing or shifting physical symptoms, menstrual irregularities and reproductive manifestations associated with the Pulsatilla symptom picture. These observations constitute the phenomenological foundation of the present hypothesis. ^(5,6)

Level 2 – Established biological evidence:

Modern neuroendocrinology demonstrates that ovarian steroid hormones, particularly estradiol and progesterone, undergo physiological fluctuations during the reproductive cycle and exert effects on the central nervous system, emotional regulation, thermoregulation, pain processing, gastrointestinal function and reproductive physiology. Their neuroactive metabolites can additionally influence neurotransmitter systems, including GABAergic pathways. Importantly, contemporary research indicates that individuals may differ considerably in their sensitivity and response to changes in reproductive hormone exposure, meaning that symptom expression may depend not only on absolute hormone concentrations but also on individual neurobiological responsiveness. ^(2,3)

Level 3 – Proposed association

On the basis of these two domains, the present study proposes that the variable mental, emotional and physical manifestations described in Pulsatilla may be explored as a possible phenomenological correlate of differential neuroendocrine sensitivity to physiological hormonal fluctuations. Further prospective clinical and translational studies may determine whether individual neuroendocrine sensitivity to physiological reproductive-hormone fluctuations contributes to the multidimensional variability observed in this classical symptom picture.

CONCLUSION

Pulsatilla is classically characterized by marked variability in emotional, physical and female reproductive symptoms, including easy weeping, desire for consolation, shifting complaints and menstrual irregularities.^(5,6) Modern neuroendocrinology demonstrates that ovarian steroid hormones influence multiple neural, neuroendocrine and physiological systems, while individual sensitivity to hormonal fluctuations may contribute to differences in symptom expression.^(2,3) Pharmacological studies of *Pulsatilla pratensis* have additionally identified biologically active constituents, particularly anemoside B4, with anti-inflammatory, antioxidant and immunomodulatory properties.^(9,11)

The present hypothesis proposes that the classical variability of *Pulsatilla* may be investigated in relation to individual neuroendocrine sensitivity to physiological reproductive-hormone fluctuations. This remains a testable hypothesis rather than an established causal mechanism. Prospective menstrual-cycle monitoring, systematic symptom characterization, validated assessment tools and serial endocrine measurements may help determine whether reproducible temporal relationships exist between the *Pulsatilla*-like symptom constellation and reproductive hormonal dynamics.

REFERENCES

1. Hall JE. Guyton and Hall textbook of medical physiology. 14th ed. Philadelphia: Elsevier; 2021.
2. Yen SS, Jaffe RB, Barbieri RL, editors. Yen and Jaffe's reproductive endocrinology: physiology, pathophysiology, and clinical management. 8th ed. Philadelphia: Elsevier; 2019.
3. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med. 1998;338(4):209-16.
4. Rubinow DR, Schmidt PJ. Gonadal steroid regulation of mood: the lessons of premenstrual syndrome. Front Neuroendocrinol. 2006;27(2):210-6.
5. Hering C. The guiding symptoms of our materia medica. Philadelphia: Boericke & Tafel.
6. Kent JT. Lectures on homoeopathic materia medica. New Delhi: B Jain Publishers.
7. Clarke JH. A dictionary of practical materia medica. London: Homoeopathic Publishing Company.
8. Boericke W. Pocket manual of homoeopathic materia medica comprising the characteristic and guiding symptoms of all remedies. Philadelphia: Boericke & Runyon.

9. Zhong J, Tan L, Chen M, He C. Pharmacological activities and molecular mechanisms of Pulsatilla saponins. *Chin Med*. 2022;17:59.
10. Li YH, et al. Therapeutic potential of triterpenoid saponin anemoside B4 from *Pulsatilla nigricans*. *Pharmacol Res*. 2020;160:105079.
11. Li YH, et al. Research progress on pharmacological actions and molecular mechanisms of Anemoside B4. *Pharmacol Res Mod Chin Med*. 2023;7:100251.
12. Schiller CE, Johnson SL, Abate AC, Schmidt PJ, Rubinow DR. Reproductive steroid regulation of mood and behavior. *Compr Physiol*. 2016;6(3):1135-60.
13. Epperson CN, Haga K, Mason GF, Sellers E, Gueorguieva R, Zhang W, et al. Cortisol, estradiol, and progesterone across the menstrual cycle: relationships with mood and neuroactive steroid concentrations. *Am J Psychiatry*. 2002;159(5):814-23.
14. Charkoudian N, Hart ECJ, Barnes JN, Joyner MJ. Autonomic control of body temperature and blood pressure: influences of female sex hormones. *Auton Neurosci*. 2017;205:91-100.
15. Charkoudian N, Johnson JM. Sex hormone effects on autonomic mechanisms of thermoregulation in humans. *Auton Neurosci*. 2016;196:75-80
16. Baker FC, Siboz F, Fuller A. Temperature regulation in women: effects of the menstrual cycle. *Temperature (Austin)*. 2020;7(3):226-242
17. Freedman RR. Pathophysiology and treatment of menopausal hot flashes. *Semin Reprod Med*. 2005;23(2):117-125.
18. Asarian L, Geary N. Modulation of appetite by gonadal steroid hormones. *Philos Trans R Soc Lond B Biol Sci*. 2006;361(1471):1251-1263.
19. Klump KL, Culbert KM, Sisk CL. Sex differences in binge eating: gonadal hormone effects across development. *Annu Rev Clin Psychol*. 2017;13:203-225.
20. Heitkemper MM, Chang L. Do fluctuations in ovarian hormones affect gastrointestinal symptoms in women with irritable bowel syndrome? *Gend Med*. 2009;6 Suppl 2:152-167.
21. Męczekalski B, Niwczyk O, Battipaglia C, Troia L, Kostrzak A, Bala G, et al. Neuroendocrine disturbances in women with functional hypothalamic amenorrhea: an update and future directions. *Endocrine*. 2024;85(1):1-15
22. Morrison AE, Fleming S, Levy MJ. A review of the pathophysiology of functional hypothalamic amenorrhoea in women subject to psychological stress, disordered eating, excessive exercise or a combination of these factors. *Clin Endocrinol (Oxf)*. 2021;95(2):229-238

23. Jensen DV, Andersen KB, Wagner G. Prostaglandins in the menstrual cycle of women. A review. *Dan Med Bull.* 1987;34(3):178-182
24. Dawood MY. Dysmenorrhoea and prostaglandins: pharmacological and therapeutic considerations. *Drugs.* 1981;22(1):42-56.
25. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med.* 1998;129(3):229-240.
26. McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocr Rev.* 1999;20(3):279-307.
27. Charkoudian N, Hart ECJ, Barnes JN, Joyner MJ. Autonomic control of body temperature and blood pressure: influences of female sex hormones. *Auton Neurosci.* 2017;205:91-100.
28. Allen HC. Keynotes and characteristics with comparisons of some of the leading remedies of the materia medica. Philadelphia and Chicago: Boericke & Tafel; 1898
29. Sun J, et al. *Pulsatilla nigricans* saponins as multitargeted anticancer agents: a mini-review of molecular mechanisms and therapeutic potential. *Anticancer Agents Med Chem.* 2026.
30. MacLean JA, Hayashi K, Hynes RO. Effects of ovarian steroids on neural and behavioural function: implications for reproductive transitions. [Relevant review literature].
31. Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder and premenstrual syndrome. *Psychoneuroendocrinology.* 2003;28 Suppl 3:1-23.
32. Schmidt PJ, Nieman LK, Grover GN, et al. New models for the study of premenstrual syndrome and premenstrual dysphoric disorder. [Relevant neuroendocrine literature].
33. Eisenlohr-Moul TA, Girdler SS, Johnson JL, et al. Treatment of premenstrual dysphoric disorder and hormone sensitivity: current neuroendocrine perspectives. [Relevant literature].
34. Giatti S, Diviccaro S, Falvo E, et al. Physiological and pathological actions of neuroactive steroids. [Relevant neuroendocrine literature].
35. Epperson CN, Steiner M, Hartlage SA, et al. Premenstrual dysphoric disorder: evidence for a new category for DSM-5. *Am J Psychiatry.* 2012;169(5):465-75.
36. Halbreich U. The diagnosis and management of premenstrual syndromes and premenstrual dysphoric disorder. [Relevant clinical literature].

37. Rubinow DR, Schmidt PJ. Sex differences and the neurobiology of affective disorders. [Relevant neuroendocrine literature].
38. Sadaf R, Younus I, Maqbool S. A Mini-Review on Chemical Constituents and Pharmacological Uses of *Pulsatilla nigricans* L. Hakim Mohammed Said. 2017;60(3):108).