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Review

Cyclical Iron Homeostasis: The Role of Sex Hormones in Female Iron Regulation

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Abstract

Iron homeostasis in premenopausal women is governed by a dual regulatory architecture that has been incompletely characterized in the clinical literature. The hepcidin-ferroportin axis, established as the master regulator of systemic iron flux, operates within a second-order hormonal framework in females of reproductive age: 17β-estradiol (E2) and progesterone (P4) directly modulate hepatic hepcidin transcription, superimposing a predictable, cycle-dependent oscillation on baseline iron availability. This review summarizes the molecular mechanisms underlying this cyclical regulation. E2 suppresses hepcidin expression through estrogen receptor-dependent regulation of the *HAMP* gene, mapped in hepatocyte models to an estrogen-responsive element (ERE) half-site. Preclinical evidence also implicates a competing pathway, mediated by the G protein-coupled estrogen receptor 1 (GPR30, also designated *GPER1*) and bone morphogenetic protein 6 (BMP6), with opposing upregulatory effects on hepcidin. Progesterone has an opposing effect, raising hepcidin in women when administered exogenously, an effect attributed in preclinical models to the progesterone receptor membrane component-1 (PGRMC1). When mapped onto the menstrual cycle, these hormonal actions predict a follicular phase of enhanced iron acquisition and a luteal phase of iron restriction. We distinguish that prediction from the evidence: the predicted late luteal hepcidin maximum is not evident in cohorts sampled serially across the cycle, and circulating interleukin-6 does not rise in the luteal phase, so the cycle-level consequence of the hormonal mechanism remains the central open question. The clinical implications extend to diagnostics and therapeutics: standard iron status biomarkers fluctuate predictably with cycle phase, confounding single-time-point assessments; and the clinical significance of these fluctuations differs mechanistically depending on whether the underlying deficit reflects absolute storage depletion, impaired functional delivery, or erythropoietic cellular restriction. This review proposes a mechanism-oriented biomarker subtyping framework to address this diagnostic gap and discusses cycle-synchronized iron supplementation as a biologically plausible hypothesis that warrants rigorous evaluation in future clinical trials.

Keywords: iron deficiencies; hepcidins; menstrual cycle; estrogens; progesterone; iron; ferritins; transferrin; women's health

1. Introduction: The Fundamentals of Systemic Iron Homeostasis

Iron is among the most functionally indispensable transition metals in human physiology, serving as the catalytic core of hemoglobin, myoglobin, mitochondrial cytochromes, and a broad array of oxidoreductive enzymes [1,2,3]. Despite its essentiality, free iron is chemically hazardous: the cellular labile iron pool participates in Fenton-type reactions that generate hydroxyl radicals capable of oxidizing lipids, proteins, and nucleic acids, producing cellular damage that is particularly injurious to rapidly dividing erythroid precursors and hepatocytes [4,5,6]. The body therefore maintains iron homeostasis through a tightly regulated system of acquisition, intracellular trafficking, storage, and recycling. Unlike most micronutrients, total body iron content is controlled almost exclusively at the level of intestinal absorption; humans possess no active excretory mechanism, and obligate losses through skin desquamation, gastrointestinal epithelial shedding, and urinary excretion are largely fixed [7,8].

Dietary iron is absorbed by duodenal enterocytes in two principal forms. Non-heme iron, the dominant form in plant-based diets, is reduced at the brush border by duodenal cytochrome b (Dcytb) and transported across the apical membrane by the divalent metal-ion transporter 1 (DMT1, encoded by *SLC11A2*) [8]. Heme iron, derived from myoglobin and hemoglobin in animal-source foods, is internalized via a distinct receptor-mediated pathway and metabolized intracellularly to release Fe^{2+} into the same labile iron pool [7]. Inside the enterocyte, iron is either stored as ferritin or exported across the basolateral membrane into the portal circulation by ferroportin (FPN1, encoded by *SLC40A1*), the sole known mammalian cellular iron exporter [7,8].

However, dietary absorption accounts for only 1 to 2 mg of the 20 to 25 mg of iron required daily for ery-

thropoiesis and other physiological functions. The majority of this daily requirement is met by macrophages of the reticuloendothelial system, which phagocytose senescent red blood cells, catabolize hemoglobin, and export the recovered iron back into circulation via ferroportin for reuse by erythroid precursors [7,9]. This recycling pathway is the dominant source of iron for hemoglobin synthesis under physiological conditions and represents the mechanistic node at which systemic iron availability is most acutely sensitive to regulatory signals.

The evidence underpinning the mechanisms described in this review spans three tiers, and the distinction matters for clinical interpretation. Direct evidence from controlled human studies represents the strongest tier; preclinical *in vivo* and *in vitro* work constitutes a second tier of mechanistic plausibility; and inference from physiology, while a legitimate analytical tool, is the weakest. Where claims in this review rely on a particular tier, we have aimed to make that explicit in context.

1.1 Hepcidin as the Master Regulator

The discovery of hepcidin, a 25-amino acid cysteine-rich peptide hormone synthesized predominantly by hepatocytes, established the unifying molecular logic of systemic iron regulation [10,11,12]. Hepcidin binds directly to ferroportin on the surface of enterocytes, macrophages, and hepatocytes, inducing its ubiquitination, internalization, and lysosomal degradation [10,13]. The functional consequence is mechanistically direct: elevated hepcidin depletes ferroportin from cellular surfaces, simultaneously blocking intestinal iron absorption and reticuloendothelial iron recycling, thereby restricting iron delivery to plasma. Conversely, when hepcidin is suppressed, ferroportin is stabilized, iron export proceeds unimpeded, and systemic iron availability increases [10].

The transcriptional regulation of the *HAMP* gene (which encodes hepcidin) integrates multiple physiological inputs. Under iron-replete conditions, bone morphogenetic protein 6 (BMP6) and BMP2 secreted by liver sinusoidal endothelial cells activate a SMAD1/5/8 phosphorylation cascade; phosphorylated SMAD1/5/8 complexes with SMAD4 and translocates to the nucleus to drive *HAMP* transcription [10]. This iron-sensing pathway operates through membrane-bound hemojuvelin (HJV) as a co-receptor and is modulated by matriptase-2 (encoded by *TMPRSS6*), which cleaves HJV to attenuate BMP/SMAD signaling when iron demand is elevated [10]. Inflammatory stimuli, particularly interleukin-6 (IL-6) released during infection or tissue injury, activate *HAMP* transcription via a distinct Janus kinase-signal transducer and activator of transcription 3 (JAK-STAT3) pathway, producing the hypoferremia characteristic of chronic inflammation [14,15]. Erythropoietic demand suppresses hepcidin through erythroferrone (ERFE), a hormone released by erythroblasts that acts as a ligand trap for BMP5, BMP6, and BMP7, thereby impairing hepatic BMP/SMAD signaling and prioritizing iron supply to the bone marrow during accelerated red cell production [10,16,17].

The hepcidin-ferroportin axis provides a coherent regulatory solution for organisms whose iron requirements are relatively stable over time. For premenopausal females, however, this framing is incomplete. Women of reproductive age experience cyclical, predictable fluctuations in iron demand and hormonal environment that impose a distinct second-order regulatory pattern on the baseline hepcidin set-point, which is itself lower in premenopausal women than in men and postmenopausal women [18]. The sections that follow develop this argument, beginning with the physiological iron burden created by menstruation and proceeding through the molecular mechanisms by which sex steroids reshape iron homeostasis across the menstrual cycle.

1.2 Literature Search Strategy

This article is a narrative review. Relevant literature was identified through searches of PubMed/MEDLINE, Scopus, and Web of Science, supplemented by hand-searching the reference lists of key articles. Search terms combined controlled vocabulary and free-text keywords for iron metabolism and female reproductive physiology, including “iron”, “hepcidin”, “ferroportin”, “ferritin”, “transferrin saturation”, “menstrual cycle”, “estrogen”, “progesterone”, “heavy menstrual bleeding”, and “iron deficiency”. English-language human studies were prioritized; preclinical studies were included where they provided mechanistic evidence not yet available from human work and are identified as such in the text. Because the aim was an integrative mechanistic synthesis rather than a quantitative pooling of comparable studies, a formal systematic-review protocol and PRISMA flow diagram were not applied.

2. The Female-Specific Iron Burden: Menstruation and Physiological Demand

Iron deficiency is the most prevalent micronutrient deficiency worldwide, and women of reproductive age are disproportionately affected; prevalence estimates in adolescent and young adult females in industrialized populations approach 40% [19,20,21,22,23,24]. The iron economy of premenopausal women differs fundamentally from that of men not because of differences in the molecular machinery of iron regulation, but because of a recurring, obligate iron loss that operates outside the body’s capacity for homeostatic adjustment. That loss is menstruation.

2.1 The Cost of Menstruation

Basal iron losses in both sexes, primarily from gastrointestinal epithelial shedding, skin desquamation, and urinary excretion, average approximately 1 mg per day [8]. In premenopausal women, normal menstrual blood loss adds a further 15 to 30 mg of elemental iron per cycle,

equivalent to an additional daily demand of approximately 0.5 to 1.0 mg when averaged across a 28-day cycle [25]. This increment is physiologically significant because intestinal absorption of non-heme iron operates near its practical ceiling under replete conditions, with well-nourished adults absorbing approximately 1 to 2 mg per day regardless of dietary intake, a constraint imposed by the finite capacity of enterocyte DMT1 expression and ferroportin surface density [8]. Even when hepcidin is fully suppressed, the absorptive reserve available to buffer menstrual losses is limited, and women who consume diets marginally adequate in iron bioavailability exist in a state of sustained iron turnover that has no equivalent in male physiology.

The consequence is that menstruation functions not merely as a reproductive event but as a chronic iron sink that requires active physiological compensation. This compensation is not achieved by upregulating the absorptive machinery per se, but by hormonally suppressing the primary brake on that machinery, hepcidin, during the window in which replenishment is most urgently needed.

2.2 Heavy Menstrual Bleeding as a Multiplier

Heavy menstrual bleeding (HMB), clinically defined as blood loss exceeding 80 mL per cycle, amplifies this iron drain to a degree that frequently exceeds physiological compensatory capacity [26,27]. HMB is common, with prevalence estimates varying widely by definition and method of ascertainment, and it can increase total iron loss per cycle several-fold relative to normal menstrual losses [28,29]. A woman experiencing HMB may lose enough iron per cycle that the loss cannot be offset by dietary intake alone, even under conditions of maximal absorptive efficiency [25]. HMB is a leading cause of iron deficiency and iron deficiency anemia in women of reproductive age, particularly in high-income settings, and its high prevalence means that clinically significant iron depletion affects a substantially larger proportion of premenopausal women than screening data typically reflect [29,30,31].

The mechanistic significance of HMB in the context of this review is that it represents the upper boundary of female iron demand, where hormonal optimization of absorption is generally insufficient to prevent net depletion. Understanding these hormonal mechanisms is therefore particularly relevant in clinical contexts in which the absorptive window represents the principal buffer against ongoing iron loss.

3. Estrogen-Mediated Hepcidin Suppression: Maximizing Iron Acquisition

Among the hormonal modulators of hepcidin, 17β-estradiol (E2) is the best characterized (Fig. 1, Ref. [14,32,33,34]). Its effect on *HAMP* transcription is complex and mediated through at least two distinct molecular pathways, with the weight of current evidence strongest for a direct transcriptional suppressive mechanism.

3.1 Direct Transcriptional Suppression via the Estrogen-Responsive Element

The primary mechanism by which 17β-estradiol suppresses hepcidin transcription appears to involve estrogen receptor-dependent regulation of the *HAMP* promoter, including a functional estrogen-responsive element (ERE) half-site identified by Yang et al. [35]. In human liver cell lines, 17β-estradiol reduced *HAMP* transcription, an effect blocked by the estrogen-receptor antagonist ICI 182780. Luciferase reporter activity was decreased by E2 in a dose-dependent manner, deletion of an ERE half-site located between −2474 and −2462 bp upstream of the *HAMP* transcriptional start site abolished this repression, and electrophoretic mobility shift assays showed that nuclear proteins from E2-treated cells bound the wild-type but not the mutated half-site, supporting that site as a functional cis-regulatory element for estrogenic hepcidin suppression [35]. The receptor-level mechanism is therefore preclinical, but the underlying phenomenon has human support: in women undergoing gonadotropin stimulation for *in vitro* fertilization (n = 31), a greater than 25-fold rise in endogenous estradiol was accompanied by a fall in median serum hepcidin-25 from 4.85 to 1.43 ng/mL ($p < 0.01$), and this occurred despite a concurrent rise in C-reactive protein, which would be expected to raise hepcidin [33]. That study is an uncontrolled within-subject observation rather than a randomized estrogen intervention, and gonadotropin-driven ovarian androgen secretion may contribute, so it is best read as supportive human *in vivo* evidence rather than confirmatory.

Mechanistically, the activated estrogen receptor alpha (ERα) is thought to interact with the *HAMP* promoter in a way that reduces transcriptional activity, in part by competing with SMAD4-dependent transcriptional inputs at promoter regulatory elements [10,35]. This provides a plausible molecular link between rising E2 concentrations during the follicular phase and lower hepatic hepcidin production [35].

As E2 rises toward the late follicular phase, hepcidin suppression may enhance ferroportin availability on enterocytes and macrophages, thereby favoring intestinal iron absorption and reticuloendothelial iron recycling [10]. However, because the broader estrogen-hepcidin literature is not perfectly uniform across models and contexts, the suppression of hepcidin by estrogen should be framed as a well-supported phenomenon whose receptor-level mechanism, the ERE half-site, remains characterized principally in hepatocyte models rather than in human physiology.

3.2 GPR30-BMP6 Signaling: A Competing Preclinical Pathway

A second, contradictory pathway involves E2 signaling through the G protein-coupled estrogen receptor 1 (GPR30, also designated *GPER1*). In contrast to the suppressive ERE mechanism, Ikeda et al. [36] reported

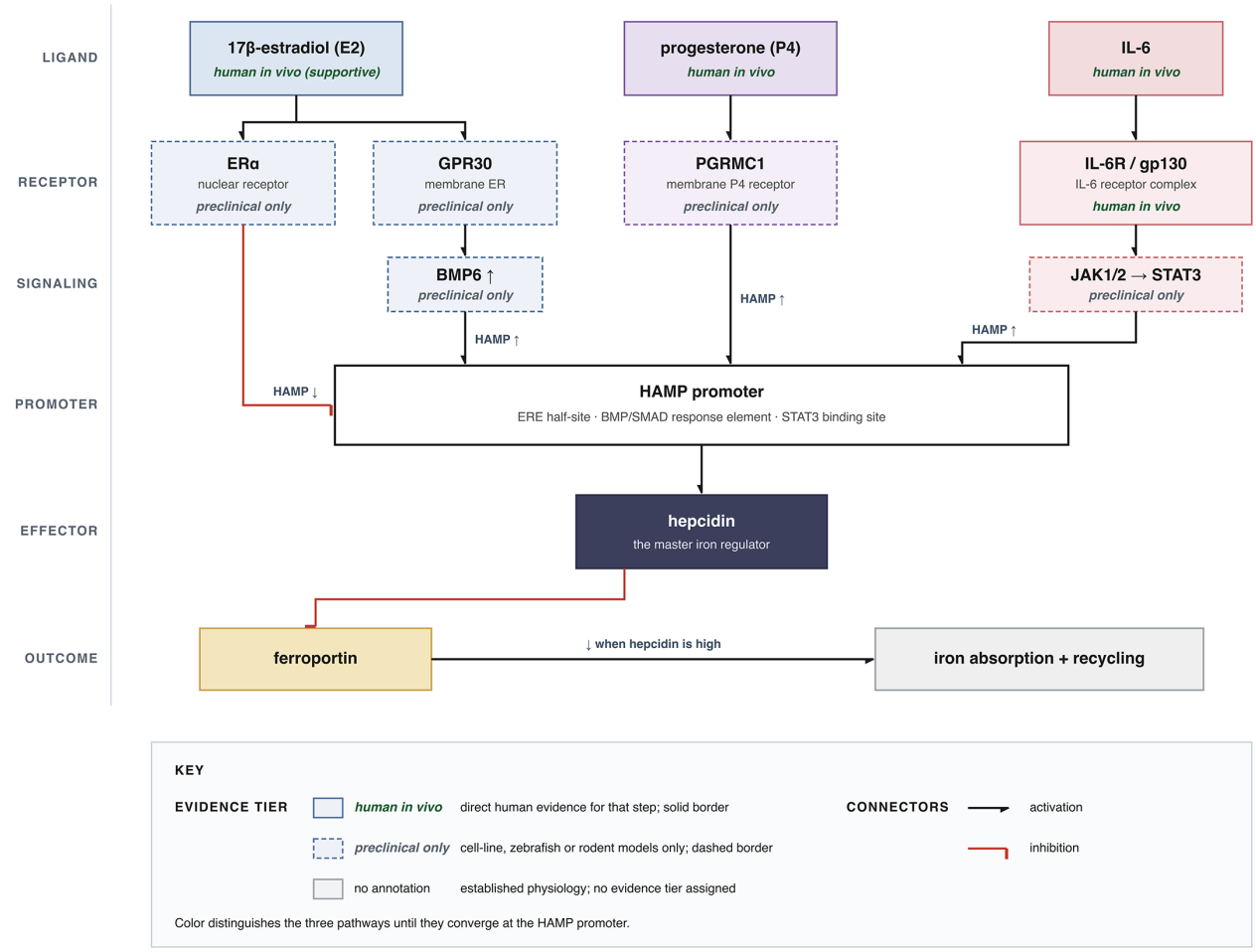

Fig. 1. Sex-steroid and inflammatory control of hepcidin transcription. Convergent and opposing hormonal and inflammatory inputs act on the *HAMP* promoter. 17β-estradiol acts through estrogen receptor alpha at an estrogen-responsive element half-site to suppress *HAMP* transcription, and through the G protein-coupled estrogen receptor 1 to induce bone morphogenetic protein 6, which opposes that suppression. Progesterone induces *HAMP* through progesterone receptor membrane component-1. Interleukin-6 induces *HAMP* through the IL-6 receptor and the JAK-STAT3 pathway. Hepcidin then binds ferroportin, reducing intestinal iron absorption and macrophage iron recycling. Evidence tiers and connector conventions are defined in the key. The ligand and receptor levels are tiered separately, because they differ. Intravenous interleukin-6 raises hepcidin and lowers serum iron in volunteers, and interleukin-6 receptor blockade lowers serum hepcidin in patients with an interleukin-6-driven disorder [14,34]. Exogenous progesterone raised serum hepcidin approximately threefold in 20 women during *in vitro* fertilization [32]. A large rise in endogenous estradiol lowered circulating hepcidin in women [33], although that observation is uncontrolled, was made at an estradiol excursion above the physiological range, and is therefore supportive rather than confirmatory.The sex-steroid receptor-level mechanisms, ERα, GPR30 and PGRMC1, rest on cell-line, zebrafish or rodent models only. The hormones therefore move hepcidin in women; the receptors through which they are proposed to do so have not been shown to do so in humans. For interleukin-6, human evidence extends to the receptor level, whereas downstream JAK-STAT3 signaling, like the intracellular nodes of the other pathways shown, derives from preclinical models. The sex-steroid arms are therefore presented as mechanisms to test, not as established human physiology. BMP6, bone morphogenetic protein 6; E2, 17β-estradiol; ERE, estrogen-responsive element; ERα, estrogen receptor alpha; GPR30, G protein-coupled estrogen receptor 1; *HAMP*, hepcidin antimicrobial peptide gene; IL-6, interleukin-6; JAK-STAT3, Janus kinase-signal transducer and activator of transcription 3; P4, progesterone; PGRMC1, progesterone receptor membrane component-1. Created with Figma.

that in ovariectomized murine models and cultured hepatocytes, estradiol *upregulates* hepcidin through induction of BMP6 via GPR30-dependent signaling. This evidence, however, is derived exclusively from preclinical *in vivo* and *in vitro* systems; whether GPR30-BMP6 upregulatory signaling counteracts ERE-mediated suppression in intact human physiology to a clinically meaningful degree has not been established in controlled human studies [37]. The ex-

istence of these competing pathways highlights the complexity of estrogenic hepcidin regulation and provides one plausible explanation for why human post-exercise and supplementation responses may differ from those predicted by animal models.

3.3 Physiological Consequence: The Follicular Absorption Window

Together, these mechanisms are predicted to produce a period of reduced hepatic hepcidin output during the follicular phase, during which the absorption and macrophage recycling pathways described above would operate at maximal efficiency. As set out in Section 5.1, this predicted follicular window is not evident in serially sampled human data. The follicular phase absorptive window is temporally coordinated with the recovery of erythropoietic capacity following the red cell losses of menstruation: estrogen rises, hepcidin falls, absorption increases, and erythropoiesis expands in a sequence consistent with a compensatory response to the monthly erythrocyte deficit.

4. Progesterone-Mediated Hepcidin Upregulation: The Luteal Restriction

Following ovulation, the hormonal environment transitions from estrogen dominance to progesterone (P4) dominance (Fig. 1). This transition has a direct opposing effect on hepcidin regulation, creating the second phase of the cyclical iron availability pattern that characterizes female iron homeostasis.

4.1 PGRMC1-Mediated Hepcidin Stimulation

Progesterone upregulates hepcidin biosynthesis through the progesterone receptor membrane component-1 (PGRMC1), a non-classical, membrane-associated progesterone receptor expressed in hepatocytes and distinct from the classical nuclear progesterone receptor (PR). Li et al. [32] reported that progesterone treatment increases *HAMP* mRNA and hepcidin protein in human hepatoma cells and in zebrafish, that PGRMC1 depletion blocks and anti-PGRMC1 antibodies attenuate this induction, and that mifepristone, a progesterone-receptor antagonist that acts through the same PGRMC1-dependent route, raises hepatic hepcidin expression approximately 2.5-fold in mice [32]. Critically, the same study provides direct human *in vivo* evidence for the ligand-level effect: in 20 women receiving exogenous progesterone during *in vitro* fertilization, serum progesterone rose from 0.31 ng/mL to 24.6 ng/mL and serum hepcidin increased approximately threefold ($p < 0.01$), an effect reproduced with a second immunoassay [32]. Progesterone therefore raises hepcidin in women. What remains preclinical is the receptor machinery, PGRMC1, through which it is proposed to do so.

As P4 rises through the mid-to-late luteal phase, PGRMC1-driven *HAMP* upregulation is expected to progressively increase circulating hepcidin. The consequence is broadly opposite to the follicular window: iron export from enterocytes and macrophages is reduced, restricting delivery to plasma and the iron available for erythropoietic use. This luteal restriction is teleologically consistent with a cycle that does not culminate in pregnancy; however, the human evidence directly linking PGRMC1 signaling to the magnitude of *in vivo* luteal hepcidin changes remains limited, and the strength of this inference rests primarily on the preclinical mechanistic data.

4.2 Inflammation as a Candidate Amplifier: IL-6 in the Luteal and Premenstrual Phases

The PGRMC1-mediated hepcidin stimulus during the luteal phase may be compounded by pro-inflammatory signaling, although the evidence for a cyclical inflammatory signal is mixed. C-reactive protein varies significantly across the menstrual cycle and is positively associated with luteal progesterone, but it is highest during menstruation and is inversely associated with estradiol [38]. Studies that measured circulating IL-6 directly do not show a luteal rise, reporting either no significant variation across the sampled cycle [39] or lower IL-6 in the luteal phase [40]. IL-6 activates *HAMP* transcription via the JAK-STAT3 pathway [14,15], and IL-6 receptor blockade lowers serum hepcidin in patients with an IL-6-driven disorder [34], so an inflammatory signal, where one is present, would add to PGRMC1-driven hepcidin induction. On the current evidence, however, no such cyclical signal is established, and the predicted late luteal hepcidin maximum therefore rests on progesterone signaling alone. An apparent paradox must be confronted here, because it defines what this framework does and does not claim. Administering progesterone to women raises hepcidin approximately threefold [32], and two studies report higher hepcidin in the mid luteal phase than in the early follicular phase [41,42], although a third found no significant cyclical variation in hepcidin at all [43]. Yet the largest cohort sampled serially across the natural cycle (n = 90, six visits per woman including one between days 26 and 29), found hepcidin to dip during menstruation, rebound to its highest sampled values in the days following it, a rebound that was small or absent in about two thirds of women, and then remain stable through the second half of the cycle [44,45]. The ligand-level effect is therefore demonstrable in women, while the predicted late luteal maximum is not evident in observational cycle data. Three considerations reconcile these observations, and each is testable. First, the progesterone concentration that raised hepcidin in the interventional setting (approximately 25 ng/mL) sits at or above the upper end of the mid luteal physiological range, which is typically 10 to 20 ng/mL, so the endogenous luteal signal may be too small to detect against background variability. Second, in the serially sampled cohort the volume of menstrual blood loss was among the covariates that influenced the fitted model pa-

rameters, so the iron-driven signal may simply dominate the hormonal one. Third, a majority of participants in that cohort used oral contraception, which blunts the endogenous luteal progesterone rise, and sex steroids were not measured in it at all. The luteal limb of this framework should accordingly be read as a mechanism that operates in women but whose contribution to the natural cycle has not yet been isolated, and which requires cohorts in which hormonal phase can be dissociated from menstrual iron loss [46].

For women who engage in regular aerobic exercise, this inflammatory hepcidin stimulus is further compounded by exercise-induced IL-6 release from contracting skeletal muscle [47,48]. Post-exercise hepcidin spikes have been documented within 3 to 6 hours of sustained aerobic effort and suppress intestinal iron absorption during a period when erythropoietic demand is elevated [47,49]. In a luteal-phase athlete, the post-exercise hepcidin increment adds a further regulatory input on top of PGRMC1 signaling, creating conditions in which iron absorption is likely to be substantially restricted. Menstrual cycle symptoms are highly prevalent in exercising women and are associated with missed training and competition [50], and iron depletion without anemia is associated with impaired endurance performance in female athletes [51].

5. The Cyclical Paradigm: Iron Availability, Biomarker Dynamics, and Mechanism-Oriented Disease Subtyping

The estrogen- and progesterone-driven mechanisms described above generate a coherent, cyclically structured pattern of iron availability that maps predictably onto the phases of the menstrual cycle. This pattern has two categories of clinical consequence: it produces systematic, phase-dependent fluctuations in iron status biomarkers that confound diagnostic interpretation; and it means that the mechanistic origin of iron depletion differs in ways that no single biomarker can resolve.

5.1 The Follicular Phase: Low Hepcidin and Maximal Iron Acquisition

During menstruation and the early follicular phase, hepcidin concentrations reflect a convergence of suppressive signals: active iron loss from menstrual bleeding, declining progesterone, and rising estrogen collectively drive hepcidin to its monthly nadir during menstrual bleeding [35,44,45,46]. In serially sampled cohorts hepcidin then rebounds to a maximum in the days immediately following menstruation, and is comparatively stable thereafter [44,45], so the low-hepcidin window is confined to menses itself rather than extending through the follicular phase as the mechanism would predict. The resulting ferroportin stability maximizes intestinal iron absorption and reticuloendothelial iron release, priming the erythropoietic system for hemoglobin resynthesis following menstrual erythrocyte losses. As E2 continues to rise through the mid-to-late follicular phase, ERE-mediated *HAMP* suppression sustains this absorptive window through ovulation.

5.2 The Luteal Phase: Rising Hepcidin and Iron Restriction

Following ovulation, PGRMC1-driven *HAMP* upregulation is predicted to begin restricting iron availability [32]. The absorptive window narrows progressively as the luteal phase advances, and any concurrent inflammatory signal reinforces this restriction through the same JAK-STAT3 route that, in pathological contexts, characterizes the anemia of chronic disease [52,53]. This mechanistic overlap between physiological luteal-phase iron restriction and pathological inflammatory iron sequestration has important implications for biomarker interpretation, addressed in the mechanism-oriented subtyping framework below.

5.3 Modifiers of the Cyclic Pattern

The cyclic hepcidin and iron biomarker pattern described above represents a canonical premenopausal physiology and is meaningfully modulated by several common clinical conditions. Combined oral contraceptives flatten the endogenous E2 and P4 oscillation, attenuating the amplitude of cycle-phase variation in iron and hepcidin without eliminating it [45]. A history of pregnancy alters baseline iron stores through gestational iron transfer and postpartum recovery, and lactation extends the period of elevated iron demand. Perimenopausal hormonal variability disrupts the predictability of the cycle, making cycle-phase-adjusted reference ranges progressively less applicable as women approach the menopausal transition. Heavy menstrual bleeding compounds the baseline iron deficit and may shift the locus of clinical concern from cycle-phase optimization to absolute repletion [26,27,29]. Chronic inflammatory disease and active infection elevate baseline IL-6 and impose hepcidin elevation independent of cycle phase, complicating both the mechanism and the diagnostic interpretation of iron status [53]. Endurance training produces repeated post-exercise IL-6 and hepcidin spikes that, in luteal-phase athletes, can amplify the physiological luteal restriction [46,47,48,49,54]. Finally, ongoing iron supplementation reshapes the hepcidin response through both the acute post-dose hepcidin spike and longer-term repletion effects [55]. Recognizing these modifiers is a prerequisite for applying the framework that follows to any individual clinical assessment.

Endocrine disorders that disrupt the ovulatory hormonal rhythm represent a further and distinct class of modifier, because they attenuate or abolish the follicular-luteal oscillation on which the framework described here depends. Polycystic ovary syndrome (PCOS), the most common endocrinopathy of reproductive-age women, is characterized by anovulation, hyperandrogenism, and insulin resistance and is associated with a disordered iron economy: circulating hepcidin is reduced, favoring increased intestinal iron

absorption and higher body iron stores [56,57], with altered expression of iron-regulatory genes also reported [58]. This androgen-associated hepcidin suppression is mechanistically consistent with experimental evidence that testosterone represses hepcidin transcription through the same BMP-SMAD axis central to this review [59]. Serum ferritin in PCOS must be interpreted with particular caution, and separately from the hepcidin axis: because ferritin is an acute-phase reactant, the chronic low-grade inflammation and insulin resistance of PCOS can raise it independently of the suppressed hepcidin set-point, and combined oral contraceptive use can raise it further, so that an elevated ferritin may coexist with a hepcidin profile that favors iron loading rather than deficiency [60]. Functional hypothalamic amenorrhea and other anovulatory states, by contrast, are marked by chronic hypoestrogenism and loss of cyclic progesterone exposure, so that the phase-dependent hepcidin pattern is absent altogether; in these women the amenorrhea also removes the recurrent menstrual iron sink. In all of these conditions the cycle-phase logic of the present framework does not apply, and iron status must be interpreted against the specific hormonal and inflammatory context of the disorder.

5.4 Biomarker Fluctuations Across the Cycle

The hepcidin oscillation described above produces predictable fluctuations in standard iron status biomarkers that carry direct implications for diagnostic accuracy (Fig. 2, Ref. [32,44,45,61]; Table 1, Ref. [44,45,61,62,63]). Iron biomarkers differ markedly in how much they fluctuate across the cycle. In cross-sectional population data, in which cycle phase was assigned from self-reported cycle day, serum iron and transferrin saturation (TSAT) vary significantly by cycle phase, being lowest during menstruation and rising to a peak in the early-to-mid luteal phase [61,64]. Serum ferritin, by contrast, is comparatively stable across cycle phases [61]; where ferritin appears elevated in the presence of inflammation, this reflects its behavior as an acute-phase reactant rather than a genuine rise in iron stores; we note that C-reactive protein is reported to be highest during menstruation rather than in the luteal phase [38], so a specifically late luteal inflammatory elevation of ferritin should not be assumed. Hemoglobin similarly shows only minor cycle-phase variation. The clinically important point is therefore that the most phase-labile markers, serum iron and TSAT, are also the most sensitive to sampling time, whereas ferritin is confounded less by cycle phase than by inflammation.

5.5 Mechanism-Oriented Disease Subtyping: Beyond Single Biomarker Thresholds

The cyclical biomarker fluctuation problem is compounded by a more fundamental diagnostic challenge: the iron biomarker panel captures information about multiple distinct physiological states, and differentiating between them requires an interpretive framework organized by mechanism rather than by threshold. Three mechanistically distinct subtypes of iron insufficiency are relevant in premenopausal women, each with a characteristic biomarker signature and distinct clinical implication.

5.5.1 Absolute Storage Depletion

Absolute storage depletion represents the exhaustion of reticuloendothelial and hepatic iron stores. The canonical biomarker is serum ferritin: a soluble protein complex that stores iron in a non-toxic form within cells and is released into circulation in proportion to intracellular iron content; low serum ferritin is the most sensitive early indicator of depleted iron stores, with recent physiologically based work suggesting thresholds higher than current World Health Organization (WHO) guidelines [62,64,65]. The practical limitation of ferritin as a diagnostic marker is its dual role as an acute-phase reactant: hepatocyte ferritin synthesis is upregulated by IL-6 and other pro-inflammatory cytokines independently of iron status, producing a ferritin elevation that reflects inflammation rather than iron repletion [62]. This is particularly consequential in women with HMB, in whom an inflammatory elevation of ferritin may mask concurrent iron loss [62].

The BRINDA (Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia) correction approach, which adjusts ferritin values for concurrent inflammatory markers, provides a partial solution to this problem at the population level [66]. However, it does not address cycle-phase ferritin variability in individual clinical assessments.

5.5.2 Functional Delivery Restriction

Functional delivery restriction refers to a state in which iron stores may be adequate or even elevated but iron delivery to tissues and erythroid precursors is impaired. The mediator is elevated hepcidin, which represents the basis of the anemia of chronic inflammation; in premenopausal women a physiological variant is proposed during the luteal phase from PGRMC1-driven hepcidin elevation, and a pathological variant can arise from sustained IL-6 elevation from infection, autoimmune disease, or heavy training [52,53].

The biomarkers that best capture functional delivery restriction are TSAT and serum iron, both of which reflect iron actually circulating in the transport-bound form and available for cellular uptake [64]. Low TSAT in the presence of normal or elevated ferritin is the characteristic signature of functional iron deficiency (FID), distinguishing it from absolute depletion. A TSAT below 20% with a ferritin above 30 µg/L in a woman with clinical features of iron deficiency should prompt evaluation of inflammatory markers, rather than empirical iron supplementation, which will be poorly absorbed in the context of elevated hepcidin regardless of dose [62].

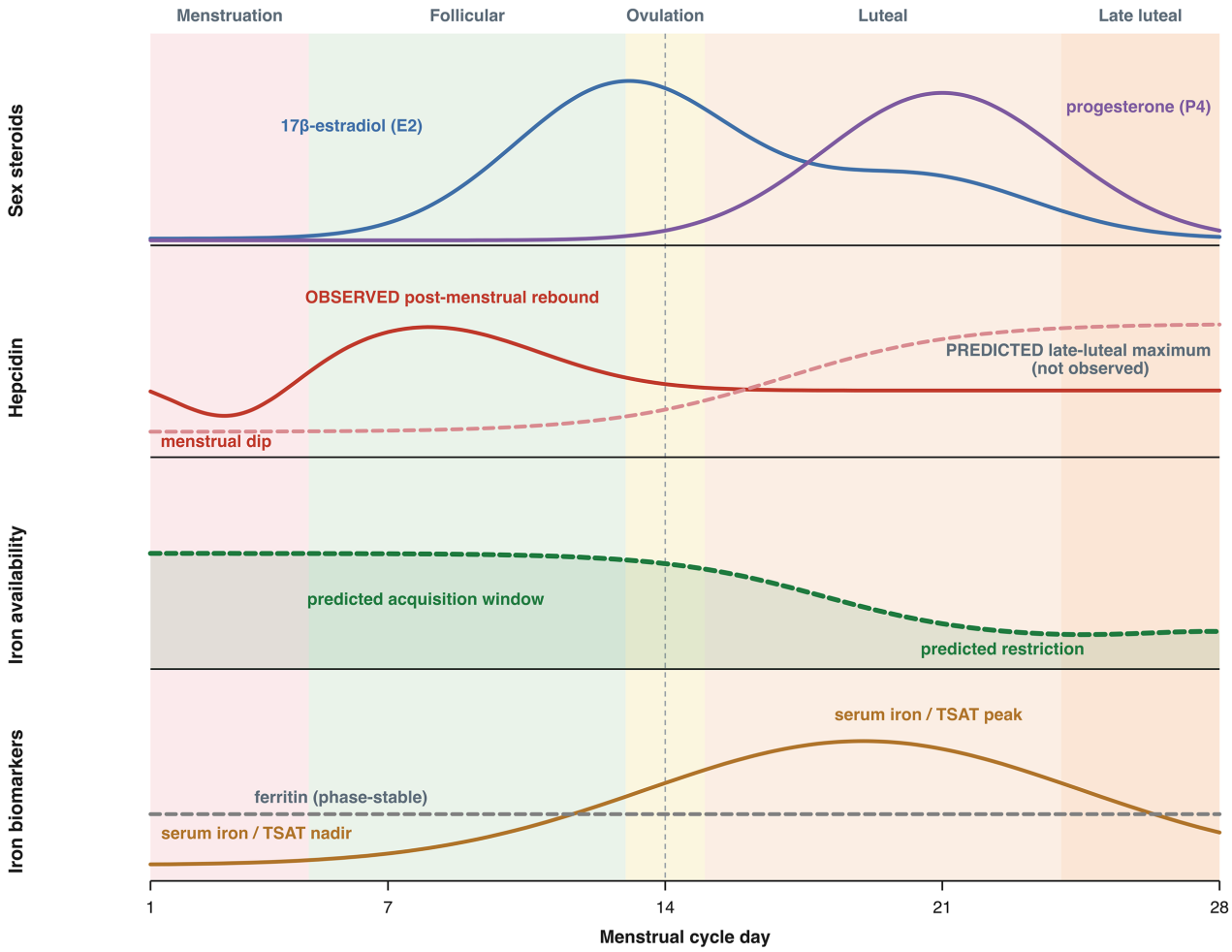

Fig. 2. Cyclical iron homeostasis across the menstrual cycle: observed biomarkers and predicted hepcidin. Four tracks are shown against cycle day: sex steroids, hepcidin, systemic iron availability, and iron biomarkers. Shaded bands denote cycle phase. The distinction between the tracks is important. The iron-biomarker track is observed: serum iron and transferrin saturation vary significantly across the cycle, being lowest during menstruation and the early follicular phase and peaking in the early-to-mid luteal phase, whereas serum ferritin is comparatively phase-stable [61]. The hepcidin track shows two curves, and the gap between them is the central open question of this review. The solid line is the trajectory observed in human serial sampling: a fall during menstruation, a rebound to a maximum in the days immediately following it, and relative stabilization through the second half of the cycle [44,45]. The dashed line is the trajectory predicted by the mechanisms reviewed here, with a late luteal maximum arising from progesterone signaling through PGRMC1 and from cycle-dependent inflammation. That predicted maximum has not been observed, even though progesterone administration raises hepcidin in women [32]; Section 4.2 sets out three testable reasons for the discrepancy. The systemic iron-availability track is dashed for the same reason: it is inferred from the predicted hepcidin trajectory, not measured. All curves are schematic and are drawn in relative units; they indicate the direction and relative timing of change, not measured values. E2, 17β-estradiol; P4, progesterone; TSAT, transferrin saturation. Created with Figma.

5.5.3 Erythropoietic Cellular Restriction

The most clinically sensitive indicators of iron insufficiency are markers of erythropoietic iron supply that reflect the iron actually available to developing erythroid precursors in the bone marrow, rather than iron in the storage or transport compartments. Two markers are particularly informative.

Soluble transferrin receptor (sTfR) is a truncated form of cellular transferrin receptor-1 (TfR1) shed into circulation in proportion to TfR1 surface expression on erythroid precursors. TfR1 expression is upregulated by iron regulatory protein 1/2 (IRP1/IRP2)-mediated mRNA stabilization when intracellular iron is limited [67,68], and because erythroid precursors are the most iron-demanding cells in the body, sTfR rises early in iron depletion, before hemoglobin or mean corpuscular volume (MCV) become

Table 1. Cyclical regulation of iron homeostasis across the menstrual cycle.

Feature	Menstruation	Days following menstruation	Late follicular/periovulatory	Early-to-mid luteal	Late luteal/premenstrual
Dominant sex steroid	Low E2, low P4	Low, then rising E2	Peak E2	Rising P4 (with secondary E2)	High P4, falling E2
Hepcidin (observed)	↓ dip (menstrual blood loss)	↑ rebound to maximum [44,45]	Declining from the rebound	Relatively stable	Relatively stable; no maximum demonstrated
Hepcidin (predicted)	↓ nadir	↓ low (E2/ERE suppression)	↓ low	→ rising (PGRMC1)	↑ maximum (PGRMC1); not observed in cycle data
Ferroportin activity/iron export	↑ maximal	↑ high	↑ high	→ declining	↓ restricted; inferred from predicted hepcidin
Absorptive capacity (predicted)	High	High	Maximal	Declining	Restricted (predicted, not measured)
Serum ferritin	Phase-stable [61]	Phase-stable [61]	Phase-stable [61]	Phase-stable [61]	Phase-stable [61]
TSAT/serum iron	↓ lowest [45,61]	↑ rebound; TSAT >45% in >13% of women [45]	Rising [61]	↑ peak [61]	Declining [61]
sTfR/CHr (erythropoietic iron supply)	sTfR highest during menstruation [61]; least confounded by inflammation [62,63]	n/a	n/a	n/a	n/a
Key modifiers	HMB amplifies loss	n/a	n/a	n/a	Exercise and chronic inflammatory disease raise IL-6 and hepcidin; combined oral contraceptives attenuate the amplitude; PCOS and anovulation attenuate or abolish the cyclic pattern

Direction of change is relative to the individual's own monthly range. The ligand-level hormonal effects on hepcidin are supported by human *in vivo* data; the receptor mechanisms (ERE half-site, GPR30-BMP6, PGRMC1) are supported principally by preclinical models. The hepcidin row is therefore split: what is observed in cohorts sampled serially across the cycle, and what the reviewed mechanisms predict. The predicted late luteal maximum is not evident in the human cycle data currently available, and the observed post-menstrual rebound was small or absent in about two-thirds of women (see text). ↓ = decreased/nadir; ↑ = increased/peak; → = transitional; n/a = not applicable (no phase-specific pattern or modifier reported). BMP6, bone morphogenetic protein 6; CHr, reticulocyte hemoglobin content; E2, 17β-estradiol; ERE, estrogen-responsive element; GPR30, G protein-coupled estrogen receptor 1; HMB, heavy menstrual bleeding; IL-6, interleukin-6; P4, progesterone; PCOS, polycystic ovary syndrome; PGRMC1, progesterone receptor membrane component-1; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

abnormal [62,64]. Critically, sTfR is not elevated by inflammation in the same way as ferritin, making it a more specific indicator of true tissue iron deficiency in the context of concurrent inflammatory conditions or luteal-phase ferritin elevation [62,63].

Reticulocyte hemoglobin content (CHr, or Ret-He) measures the hemoglobin concentration in newly released reticulocytes, providing a real-time index of the iron supply available to erythroid precursors during their final maturation over the preceding three to four days [64]. Because reticulocytes carry the hemoglobin synthesized under the iron conditions present during their maturation, CHr reflects current erythropoietic iron supply more acutely than either ferritin or sTfR. A CHr below 28 pg is indicative of iron-restricted erythropoiesis regardless of ferritin status and can identify functional iron insufficiency that precedes detectable changes in MCV or hemoglobin concentration [64].

Together, sTfR and CHr provide a window into the cellular iron economy that is largely independent of the storage and transport compartments captured by ferritin and TSAT. Distinguishing between absolute depletion (low ferritin, elevated sTfR, low CHr), functional restriction (normal or elevated ferritin, low TSAT, elevated sTfR, low

CHr), and early recovery (rising ferritin, normalizing sTfR, recovering CHr) enables a mechanistically grounded characterization of iron status that is substantially more informative than any single biomarker threshold applied without cycle-phase context.

In aggregate, each biomarker has a domain in which it is most informative and a domain in which it is least informative. Ferritin is most informative as an index of absolute storage in the absence of inflammation and least informative in the presence of inflammation, where it may be falsely elevated. TSAT and serum iron are most informative for functional delivery and most subject to acute cycle-phase fluctuation, with serum iron varying meaningfully between menstruation and the luteal phase. Soluble transferrin receptor is most informative for cellular erythropoietic restriction and least confounded by concurrent inflammation, although it is not phase-invariant either, having been reported as highest during menstruation [61], making it particularly useful in women with HMB or chronic inflammatory comorbidity. Reticulocyte hemoglobin content is most informative as a real-time index of erythroid iron supply and least informative as an indicator of cumulative storage status. Reliance on any single biomarker without cycle-phase context carries a categorical risk of misclassification in either direction.

5.6 Limitations and Heterogeneity in Cycle Physiology

Several caveats temper the framework described above. Cycle physiology in premenopausal women is heterogeneous in length, hormone amplitude, and ovulatory regularity, and the canonical 28-day cycle with predictable follicular and luteal phases is an idealization that applies imperfectly to any individual. Anovulatory cycles, subclinical luteal phase deficiency, contraceptive use, perimenopausal hormonal variability, and pregnancy history all attenuate or distort the hormonal oscillation and the corresponding hepcidin pattern, and the magnitude of these effects *in vivo* is incompletely quantified [20,45]. Direct human evidence linking the molecular mechanisms reviewed above to the magnitude of cycle-phase biomarker variation remains limited, and several of the preclinical findings, notably the GPR30-BMP6 pathway, are heterogeneous or contradictory across model systems [36,37]. The framework presented here should therefore be read as an integrative hypothesis that organizes the available literature, not as a settled mechanistic account; further well-controlled human studies, ideally in cohorts stratified by cycle phenotype, contraceptive status, and training load, will be necessary to refine which components generalize and at what magnitude.

Two of the mechanisms central to this synthesis rest predominantly on preclinical data and warrant explicit caution. The estrogen-GPR30-BMP6 pathway derives from ovariectomized-rodent and cultured-hepatocyte models and is heterogeneous across systems; it acts on BMP6, the key endogenous ligand of the hepcidin-regulatory BMP-SMAD axis [69]. PGRMC1-mediated hepcidin induction has similarly been demonstrated principally in hepatocyte systems, with the magnitude of any corresponding luteal effect in women not yet directly quantified. These pathways should therefore be read as mechanistically plausible contributors whose human relevance and effect size await confirmation, rather than as established determinants of the cycle-phase pattern. We note in the same spirit that the predicted late luteal hepcidin maximum is not supported by the human data. The largest serially sampled cohort found hepcidin to peak in the days following menstruation and to be stable through the second half of the cycle [44,45], although in that cohort the variation tracked menstrual blood loss, a majority of women used oral contraception, and sex steroids were not measured, so a hormonal contribution could not be isolated. The luteal limb of this framework is therefore a mechanistic prediction rather than an observed feature of human physiology, and it is the claim most in need of direct measurement [46].

5.7 Integrative Diagnostic Approach

The framework proposed above suggests that iron status assessment in premenopausal women is most informative when based on a panel incorporating ferritin (with awareness of inflammatory confounding), TSAT (for functional delivery), and either sTfR or CHr (for erythropoietic cellular supply), ideally collected with knowledge of menstrual cycle phase. Serum iron and TSAT are lowest during menstruation and highest in the early-to-mid luteal phase [61]; consequently, a measurement taken without reference to cycle phase can misclassify iron status in either direction: an early-follicular sample may overstate deficiency, whereas a luteal sample may understate it. The implication is not to bias sampling toward the biomarker peak, which would raise specificity at the expense of the sensitivity most needed when screening an already under-detected deficiency, but to record cycle phase at the time of sampling and interpret each marker against its expected phase behavior. Ferritin, being comparatively phase-stable, remains the most robust single storage marker when inflammation is accounted for [29,64]. Operationalizing this approach does not require hormonal assays or cycle-tracking applications; patient-reported cycle day at the time of blood sampling would be sufficient to enable phase-aware interpretation. This proposal would itself benefit from prospective evaluation against current single-time-point practice.

We emphasize that the phase-aware interpretation proposed here is a reasoned framework derived from the observed direction and magnitude of biomarker change, not an established screening standard: no prospective study has yet compared phase-aware against phase-agnostic interpretation for diagnostic accuracy, and the approach should be regarded as hypothesis-generating pending such validation. The clinical cost of ignoring cycle phase is not hypothetical,

and it has been quantified. In the largest serially sampled cohort, transferrin saturation exceeded 45%, the threshold that triggers hemochromatosis gene (HFE) genotyping in screening, in more than 13% of women when blood was drawn in the days immediately following menstruation, the window in which serially sampled hepcidin and iron also rebound to their maximum, compared with only 1% during menstruation and at the end of the cycle; conversely, 29% of participants had serum iron below the normal range when sampled during menstruation [45]. We note that the serially sampled cohort [45] and the cross-sectional population data [61] locate the maximum of serum iron and transferrin saturation differently, in the days following menstruation and in the early-to-mid luteal phase respectively. That discrepancy is itself instructive, and it is a further reason why the phase of sampling should be recorded and interpreted rather than a single optimal window selected. Phase-blind sampling therefore generates both unnecessary genotyping and spurious iron deficiency in the same population, depending only on the day of the draw. On the strength of these data the authors recommended that hepcidin and iron-status parameters be measured not during menstruation or the days that follow, but during the last five days of the cycle [45]. It is important to be precise about why. That window is proposed because concentrations are most stable there, not because they are highest; it is a low-variance window, not a biomarker peak, and the two are not the same recommendation. We do not propose sampling be biased toward any biomarker maximum, for the reason given above. What the framework advanced here requires is only that the phase of sampling be known and interpreted, and the practical value of a low-variance window is that it makes that interpretation less sensitive to the exact day of the draw.

6. Conclusions and Clinical Implications

The evidence reviewed here indicates that iron homeostasis in premenopausal women is unlikely to be a static physiological parameter that can be reliably assessed against a fixed reference range. The available literature is most readily explained by a dynamically regulated system governed by the interplay of cyclically fluctuating sex steroids, the recurring iron demands of menstruation, and the inflammatory milieu of specific cycle phases, producing oscillations in hepcidin activity and iron bioavailability with potential consequences for both diagnostic interpretation and therapeutic timing.

6.1 Cycle-Synchronized Supplementation: A Hypothesis for Future Trials

Before developing this hypothesis, it is worth stating plainly what is and is not supported by trial-level evidence. Randomized data support the efficacy of oral and intravenous iron for iron deficiency in women [70,71,72,73,74,75,76], and support dosing strategies that exploit the acute post-dose hepcidin spike, namely alternate-day and morning dosing [55,77,78,79]. What has not been tested in any randomized trial is whether timing supplementation to the follicular hormonal window improves repletion. The following paragraphs therefore extend an evidence-based dosing principle into a mechanistically plausible but currently untested cycle-scale hypothesis.

The mechanistic evidence reviewed here is compatible with the hypothesis that premenopausal women may be more responsive to oral iron supplementation during the follicular phase, when E2-driven hepcidin suppression through the ERE pathway may favor ferroportin availability and absorptive efficiency [35]. On this account, supplemental iron delivered during this window might encounter relatively less hepcidin-mediated resistance at the enterocyte basolateral membrane. Conversely, iron delivered during the late luteal phase could plausibly be restricted by the combined effects of PGRMC1-driven and IL-6-driven hepcidin elevation, regardless of dose and formulation [32,55]. Each step in this logic is mechanistically supported but not directly validated *in vivo*, and the magnitude of any phase-dependent absorption difference in humans remains unknown.

Cycle-synchronized supplementation is presented here as a hypothesis derived from the mechanisms reviewed, not as an evidence-based recommendation. No published randomized controlled trial has directly compared follicular-phase versus luteal-phase iron supplementation in terms of clinical iron repletion outcomes. What exists is robust mechanistic evidence for the hepcidin-mediated absorptive mechanism, combined with randomized controlled trial data supporting alternate-day dosing strategies that exploit the acute post-dose hepcidin spike [55,77,78] and time-of-day approaches that exploit the diurnal hepcidin nadir [79]. Independent of cycle timing, a substantial body of trial and meta-analytic evidence supports oral and intravenous iron supplementation for iron deficiency in women, both with and without anemia [70,71,72,73,74,75,76]. In athletes specifically, randomized and meta-analytic data indicate that supplementation can improve ferritin, performance, and fatigue endpoints in iron-deficient non-anemic individuals [80,81,82,83,84,85]. Cycle-synchronized dosing extends this logic from the 24-hour post-dose hepcidin window to the 14-day hormonal window of the follicular phase, but this extension has not been formally tested. The hypothesis is biologically plausible and the mechanistic rationale is sufficient to justify a well-designed trial, but clinicians should not implement phase-specific supplementation protocols as evidence-based guidelines without that trial-level evidence.

6.2 Standardizing Diagnostic Screening by Cycle Phase

A cycle-phase-aware approach to iron screening in premenopausal women would not require new technology,

but only that clinicians document cycle day at the time of blood sampling and interpret results in light of phase-dependent biomarker behavior [44,45,64,86]. The clinical value of this approach over current single-time-point practice would itself need to be evaluated in prospective work. Applying identical reference ranges to women regardless of cycle phase introduces a predictable and correctable source of diagnostic variability, in a context where screening practice already appears to under-detect iron deficiency in exercising women and in adolescent and reproductive-age females [21,87]. Existing screening and laboratory guidelines [88,89,90] do not currently incorporate cycle phase as an interpretive variable, and recent work exploring machine-learning approaches to iron deficiency detection in primary-care data has similarly omitted this dimension [91].

Current international guidance continues to rely on fixed thresholds interpreted without reference to cycle phase. The World Health Organization guideline on ferritin concentrations defines iron deficiency by serum ferritin below fixed cut-offs and recommends upward adjustment in the presence of inflammation [92], and the 2024 WHO update on hemoglobin cutoffs for defining anemia similarly applies population-level thresholds [93]; neither incorporates the systematic cycle-phase variation in iron biomarkers described in this review. Recent work has argued that these fixed thresholds understate iron deficiency, proposing higher physiologically based ferritin cut-offs [94,95], while evaluations of inflammation-adjustment methods, including the BRINDA approach, continue to refine how ferritin should be interpreted where inflammation is present [96].

Beyond individual clinical assessment, this has implications for the design of epidemiological studies and clinical trials involving female participants. Studies that sample iron biomarkers at enrollment without cycle-phase documentation are effectively measuring a composite of physiological states rather than a stable baseline, introducing variance that can dilute effect estimates and may affect prevalence data for iron deficiency in women. Cycle-phase documentation is therefore recommended as a methodological consideration in studies where iron status is a primary outcome in premenopausal women.

6.3 Future Directions

Several priorities follow from this synthesis. First, the magnitude of cycle-phase variation in iron biomarkers should be quantified prospectively in cohorts stratified by cycle phenotype, contraceptive status, and training load, using serial within-individual sampling anchored to biochemically confirmed cycle phase. Second, the phase-aware interpretive framework proposed here should be tested directly against current phase-agnostic practice for its effect on classification accuracy, and the predicted late luteal rise in hepcidin should be measured directly, in designs that separate hormonal phase from menstrual iron loss. Third, the central therapeutic hypothesis, that follicular-phase supplementation encounters less hepcidin-mediated resistance than luteal-phase supplementation, warrants a randomized controlled trial comparing phase-timed dosing against standard and alternate-day regimens. Fourth, the preclinical GPR30-BMP6 and PGRMC1 mechanisms require confirmation in human physiology. Finally, epidemiological studies and clinical trials in premenopausal women should document cycle phase at the time of iron-biomarker sampling as a standard methodological practice, so that phase-driven variance is not misattributed to the exposure or intervention under study.

6.4 Summary

The hepcidin-centric model of iron homeostasis, while mechanistically robust, has largely been developed in male experimental systems and applied to female populations without explicit accounting for the hormonal layer of regulation that cyclically reshapes it [30,97]. This review has aimed to consolidate the molecular, clinical, and methodological case for integrating cycle phase into iron biomarker interpretation, diagnostic frameworks, and therapeutic timing. Continued investigation in these areas, particularly through cycle-phase-aware clinical and epidemiological study designs, should improve the validity and utility of iron assessment in the population most affected by iron deficiency globally [19,22,98].

Abbreviations

BMP, bone morphogenetic protein; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CHr, reticulocyte hemoglobin content; CRP, C-reactive protein; DMT1, divalent metal-ion transporter 1; Dcytb, duodenal cytochrome b; E2, 17β-estradiol; ERFE, erythroferrone; ERE, estrogen-responsive element; ERα, estrogen receptor alpha; FPN1, ferroportin 1; GPR30/*GPER1*, G protein-coupled estrogen receptor 1; *HAMP*, hepcidin antimicrobial peptide gene; HJV, hemojuvelin; HMB, heavy menstrual bleeding; IL-6, interleukin-6; IRP, iron regulatory protein; JAK-STAT3, Janus kinase-signal transducer and activator of transcription 3; MCV, mean corpuscular volume; P4, progesterone; PCOS, polycystic ovary syndrome; PGRMC1, progesterone receptor membrane component-1; SMAD, small mothers against decapentaplegic; sTfR, soluble transferrin receptor; TfR1, transferrin receptor 1; TSAT, transferrin saturation; WHO, World Health Organization.

Author Contributions

CD conceived and designed the review. DB, HB, and FD contributed equally to the literature search and preliminary drafting. CD revised, expanded, and finalized the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Declaration of AI and AI-Assisted Technologies in the Writing Process

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