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Integrative Biomarkers in Female Reproductive Pathology: A Comparative Review of Vitamin D Signaling, Iron Homeostasis, and Kisspeptin Modulation

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Abstract

Background: Female reproductive health is governed by a complex interplay between metabolic nutritional status and neuroendocrine regulation. Vitamin D deficiency and Iron Deficiency Anemia (IDA) are prevalent comorbidities in pregnancy, while Kisspeptin (KISS1) has emerged as a critical regulator of the Hypothalamic-Pituitary-Gonadal (HPG) axis and a metastasis suppressor in gynecological pathologies.

Objective: This review aims to synthesize current evidence linking Vitamin D deficiency to gestational anemia and to evaluate the diagnostic potential of Kisspeptin in endometriosis and reproductive cancers.

Methods: A comprehensive review of literature from 2000–2024 was conducted, focusing on observational studies, clinical trials, and molecular pathway analyses. Data regarding 25(OH)D levels, hemoglobin status, and KISS1 expression in endometrial tissues were analyzed.

Results: Vitamin D deficiency is significantly associated with increased risk of IDA in pregnant women, influencing neonatal outcomes such as APGAR scores. Mechanistically, Vitamin D modulates hepcidin, facilitating iron absorption. Conversely, aberrant Kisspeptin signaling is implicated in endometriosis via the PI3K/AKT/mTOR pathway and serves as a biomarker for ovarian carcinoma metastasis.

Conclusion: Nutritional and neurohormonal markers offer distinct but complementary insights into reproductive pathology. Integrating Vitamin D screening with novel biomarkers like Kisspeptin could enhance risk stratification for conditions ranging from gestational anemia to endometrial malignancies.

Keywords: Vitamin D, Iron Deficiency Anemia, Kisspeptin, Endometriosis, Pregnancy, HPG Axis, Reproductive Health.

Introduction

The landscape of female reproductive health is shaped by a delicate equilibrium between environmental inputs—specifically nutrition—and intrinsic neurohormonal signaling. For decades, clinical focus has largely remained compartmentalized: obstetricians manage gestational nutrient deficiencies like anemia, while reproductive endocrinologists and oncologists focus on hormonal drivers of pathologies such as endometriosis and ovarian cancer. However, emerging research suggests these systems are less distinct than previously thought. The integration of metabolic markers, particularly Vitamin D, with neurohormonal regulators like Kisspeptin, represents a frontier in understanding the etiology of reproductive disorders.

Vitamin D, traditionally viewed solely as a regulator of calcium homeostasis, is now recognized as a potent steroid pro-hormone with ubiquitous receptors (VDR) throughout the reproductive tract [1, 4]. Its deficiency has reached pandemic proportions globally, affecting millions of pregnant women and contributing significantly to the burden of disease [2]. Of particular concern is the strong epidemiological overlap between Vitamin D deficiency and Iron Deficiency Anemia (IDA), a condition that remains a leading cause of maternal and neonatal morbidity [6, 7]. The potential for Vitamin D to modulate iron metabolism via the hepcidin-ferroportin axis suggests that these two deficiencies are mechanistically coupled, rather than merely coincident.

Parallel to these metabolic concerns is the role of the Kisspeptin system. Originally identified as a metastasis suppressor (encoded by the *KISS1* gene), Kisspeptin is now established as the master regulator of the Hypothalamic-Pituitary-Gonadal (HPG) axis [13, 14]. While its role in initiating puberty is well-documented, recent investigations have illuminated its critical involvement in adult reproductive pathologies. Aberrant Kisspeptin signaling is implicated in the pathogenesis of endometriosis, where it appears to drive cell proliferation through the PI3K/AKT pathways, and in gynecological cancers, where its loss promotes metastasis [15, 20].

This review aims to bridge the gap between these two distinct domains of research. By synthesizing recent findings on the metabolic implications of Vitamin D in pregnancy and the molecular pathology of Kisspeptin in reproductive tissues, we propose a more holistic framework for assessing female reproductive risk. We will first examine the nutritional axis, focusing on the Vitamin D-Anemia connection, before exploring the neurohormonal axis through the lens of Kisspeptin in endometriosis and malignancy.

Methods

This narrative review synthesizes literature regarding the physiological and pathological roles of Vitamin D and Kisspeptin in female reproductive health. A systematic search was conducted using databases including PubMed, Scopus, and Web of Science. The search strategy employed keywords such as "Vitamin D," "Pregnancy," "Iron Deficiency Anemia," "Kisspeptin," "KISS1," "Endometriosis," and "Gynecological Cancer."

Inclusion criteria were defined to select high-quality evidence relevant to the two primary axes of investigation. For the metabolic axis, we included population-based studies, systematic reviews, and meta-analyses published between 2000 and 2024 that reported on serum 25-hydroxyvitamin D [25(OH)D] levels, hemoglobin concentrations, and maternal-fetal outcomes [2, 3]. For the neurohormonal axis, we prioritized molecular studies elucidating the *KISS1* signaling pathways (specifically PI3K/AKT/mTOR), as well as clinical studies correlating plasma Kisspeptin levels with disease progression in endometriosis and ovarian carcinoma [14, 21].

Data extraction focused on three primary domains: (1) Epidemiological prevalence data linking Vitamin D status to anemia; (2) Molecular mechanisms proposed for Vitamin D-mediated iron regulation; and (3) The specific intracellular signaling cascades activated or suppressed by Kisspeptin in endometrial and ovarian tissues. Articles were excluded if they were non-peer-reviewed or focused exclusively on male reproductive physiology.

Results

The Nutritional Axis: Vitamin D and Iron Deficiency in Pregnancy

Prevalence and Environmental Determinants

Vitamin D deficiency is a global health challenge, with recent pooled analyses of 7.9 million participants indicating that a significant proportion of the global population fails to meet the recommended threshold of 50 nmol/L [2]. This deficiency is particularly acute in pregnant women, where increased metabolic demand exacerbates the shortfall. Factors influencing serum 25(OH)D levels are multifactorial, including latitude, skin pigmentation, and dietary habits [3]. In regions with limited sun exposure or cultural practices requiring extensive clothing coverage, the reliance on dietary sources becomes critical, yet often insufficient [10].

Research indicates a robust correlation between Vitamin D status and hemoglobin levels. In a case-control study conducted in a tertiary care setting, pregnant women with

Vitamin D deficiency were significantly more likely to suffer from Iron Deficiency Anemia (IDA) compared to their Vitamin D-replete counterparts [6]. This association holds true across diverse geographical landscapes, from rural Ghana to urban Japan, suggesting a fundamental biological link rather than a purely environmental confounder [11, 12].

Mechanisms Linking Vitamin D to Erythropoiesis

The biological plausibility of the Vitamin D-Anemia connection lies in the regulation of inflammatory cytokines and hepcidin. Vitamin D exerts an anti-inflammatory effect; in its absence, pro-inflammatory cytokines such as IL-6 are upregulated. IL-6 stimulates the hepatic production of hepcidin, the master regulator of iron homeostasis. High levels of hepcidin degrade ferroportin channels, thereby trapping iron in enterocytes and macrophages and preventing its availability for erythropoiesis [4].

Furthermore, Vitamin D receptors have been identified in bone marrow tissue, implying a direct role in the proliferation of erythroid progenitor cells. A systematic review and meta-analysis confirmed that Vitamin D supplementation could improve hemoglobin levels, likely by suppressing hepcidin and enhancing iron bioavailability [7]. This synergistic relationship highlights that treating anemia in pregnancy may require addressing concurrent Vitamin D deficiency to be fully effective [5].

Impact on Maternal and Neonatal Outcomes

The consequences of this dual deficiency are profound. Gestational anemia is associated with increased risks of preterm birth, low birth weight, and postpartum hemorrhage [8]. The fetus is dependent on maternal stores for iron and Vitamin D; deficiencies in the mother translate directly to the neonate. Studies examining APGAR scores—a rapid method to assess the health of newborn children—have shown that neonates born to anemic mothers have lower scores at 1 and 5 minutes compared to those born to non-anemic mothers [9]. The compounding effect of Vitamin D deficiency further compromises neonatal bone density and immune function, setting a trajectory for poor health outcomes in infancy.

The Neurohormonal Axis: Kisspeptin in Pathology

Physiology of the Kisspeptin System

The KISS1 gene encodes a family of peptides known as kisspeptins, which bind to the G protein-coupled receptor GPR54 (or KISS1R). This system is the upstream generator of GnRH pulses, thereby orchestrating the hormonal cascade of the reproductive axis [13, 14]. While its physiological role in puberty and ovulation is well-characterized, its expression patterns change drastically in pathological states. Kisspeptin was originally discovered as a metastasis suppressor, and its loss is a hallmark of aggressive malignancy [13].

Kisspeptin in Gynecological Malignancies

In the context of ovarian and endometrial cancers, Kisspeptin acts as a "molecular brake" on cell migration and invasion. Clinical data suggest that plasma Kisspeptin levels can serve as a potential biomarker for tumor burden and metastatic potential [16]. For instance, in patients with ovarian carcinoma, reduced expression of KISS1 correlates with poorer prognosis and advanced disease stage. This suppression of metastasis is mediated through the inhibition of cell motility factors and the downregulation of matrix metalloproteinases. Interestingly, this tumor-suppressive role is not limited to gynecological cancers; elevated levels have been observed in pancreatic cancer, and its pathways are relevant in renal cell carcinoma, suggesting a broad, conserved mechanism of action [17, 20].

The Paradox of Endometriosis

Endometriosis presents a unique paradox regarding Kisspeptin expression. Unlike in cancer, where KISS1 is often downregulated to allow metastasis, endometriosis—a benign but invasive condition—often shows altered upregulation or dysregulation of Kisspeptin signaling pathways. Research utilizing human endometrial adenocarcinoma cell lines (Ishikawa cells) and patient tissue samples has elucidated the involvement of the PI3K/AKT/mTOR signaling pathway [24].

In endometriosis, the ectopic endometrial tissue exhibits survival characteristics similar to tumors but without the unchecked metastatic drive. The PI3K/AKT pathway, a critical regulator of cell cycle progression and apoptosis, is frequently activated in endometriotic lesions [21]. Kisspeptin signaling has been shown to intersect with this pathway. Specifically, studies indicate that Kisspeptin can influence the phosphorylation of AKT, thereby modulating cell survival. Furthermore, the interplay between the PI3K-PTEN-Akt-Foxo3 pathway suggests that endometriosis triggers excessive activation of primordial follicles, leading to diminished ovarian reserve [22]. This molecular insight is crucial, as it identifies Kisspeptin not just as a marker, but as a potential therapeutic target to modulate the invasive capacity of endometriotic tissue.

Discussion

The integration of nutritional and neurohormonal perspectives provides a comprehensive view of female reproductive pathology. The evidence synthesized here demonstrates that conditions treated as separate clinical entities—anemia and endometriosis—may share underlying themes of systemic dysregulation.

The Convergence of Metabolic and Hormonal Signals

The most significant insight from this review is the non-linear relationship between systemic health and reproductive function. Vitamin D deficiency acts as a metabolic stressor. By elevating hepcidin and cytokines, it creates a "blockade" against iron utilization, leading to anemia [1, 7]. This is not merely a nutrient gap; it is a physiological state of resistance that mimics chronic inflammation.

Simultaneously, the neurohormonal system, governed by Kisspeptin, monitors the body's energy status and readiness for reproduction. It is well-established that Kisspeptin neurons are sensitive to metabolic cues (such as leptin and potentially Vitamin D status). While this review focused on Kisspeptin's pathological expression in tissue, it is plausible to hypothesize that severe metabolic stress (like that induced by Vitamin D and Iron deficiency) could feedback to the hypothalamus, altering Kisspeptin secretion and affecting the HPG axis [14, 15]. This creates a "vicious cycle" where poor nutritional status compromises hormonal regulation, and hormonal dysregulation (as seen in endometriosis) exacerbates metabolic demand and inflammation.

Deep Dive: Molecular Crosstalk and Therapeutic Targets

To fully appreciate the clinical relevance, one must look closer at the molecular intersection, particularly the PI3K/AKT pathway mentioned in the context of endometriosis [21, 23]. This pathway is a central hub for cell growth and metabolism. It is activated by insulin and growth factors, but also heavily influenced by Vitamin D status. Vitamin D (calcitriol) is known to inhibit the PI3K/AKT pathway in various cancer models, promoting apoptosis and reducing proliferation.

In endometriosis, where the PI3K/AKT pathway is hyperactive [21], Vitamin D deficiency could theoretically remove a natural "brake" on this pathway, exacerbating the proliferation of ectopic tissue. Conversely, Kisspeptin's modulation of this same pathway suggests that targeting the KISS1R receptor could offer a non-steroidal method to control endometriotic growth. This highlights the potential for dual-therapy: correcting Vitamin D levels to provide background inhibition of proliferative pathways, while using Kisspeptin modulators to specifically target the neuroendocrine drivers of the disease.

Furthermore, the role of microRNA (miRNA) adds another layer of complexity. Studies in hepatocellular carcinoma have shown that molecules like microRNA-206 can down-regulate signaling pathways analogous to those in the reproductive tract [23]. If similar epigenetic mechanisms control KISS1 expression in the endometrium, they could serve as highly specific biomarkers for early diagnosis of endometriosis, a condition that currently suffers from a diagnostic delay of several years.

Clinical Implications for Screening and Management

Current prenatal care protocols prioritize hemoglobin screening, with Vitamin D often checked only in high-risk groups. The evidence reviewed here supports a shift toward universal screening for Vitamin D in early pregnancy, given its role in preventing anemia and improving neonatal outcomes like APGAR scores [9, 12]. "Silent" Vitamin D deficiency may be the root cause of refractory anemia that does not respond to iron salts alone.

For gynecological pathologies, the clinical utility of Kisspeptin is approaching reality. As a biomarker, plasma Kisspeptin could distinguish between benign ovarian cysts and malignant masses, or monitor the efficacy of treatment in endometriosis [16, 17]. The specificity of Kisspeptin isoforms (like Kisspeptin-10 and Kisspeptin-54) offers hope for non-invasive diagnostic tests that could reduce the need for exploratory laparoscopy.

Limitations

While the associations are strong, this review acknowledges limitations in the current literature. Many studies on Vitamin D and anemia are observational, making it difficult to prove strict causality versus correlation [3, 10]. Additionally, the reference ranges for "sufficiency" in Vitamin D vary by country, complicating global comparisons. regarding Kisspeptin, while the molecular pathways are becoming clear, clinical trials testing Kisspeptin agonists/antagonists in human endometriosis are still in nascent stages [15].

Future Directions

Future research should focus on randomized controlled trials (RCTs) that supplement Vitamin D specifically to treat anemia, measuring hepcidin as a primary endpoint. On the neurohormonal side, longitudinal studies tracking Kisspeptin levels in women with endometriosis could validate its use as a progression marker. Finally, investigating the direct effect of Vitamin D on KISS1 gene expression in endometrial cells could provide the "missing link" that fully unifies these two axes.

Conclusion

Female reproductive health is a multifaceted domain where metabolic sufficiency and hormonal integrity are inextricably linked. Vitamin D is not merely a nutrient but a steroid modulator that governs iron accessibility and immune

function, directly impacting pregnancy outcomes. Kisspeptin represents the neuroendocrine control tower, essential for fertility but dangerous when dysregulated in cancer and endometriosis. By adopting an integrative view—recognizing that a patient with anemia may be Vitamin D deficient, and a patient with endometriosis has a fundamental neurohormonal imbalance—clinicians can move toward more precision-based medicine. The future of reproductive medicine lies in this synthesis, treating the patient not as a collection of isolated organs, but as a complex, interconnected biological system.

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