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Clinical Limitations of Oral Contraceptives in the Management of Functional Hypothalamic Amenorrhea in Female Athletes

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Abstract

Background: Functional hypothalamic amenorrhea (FHA) is a common cause of secondary amenorrhea, typically associated with low energy availability (LEA) and hypothalamic-pituitary-ovarian (HPO) axis suppression. Although combined oral contraceptives (COCs) are frequently prescribed to mitigate bone mineral density (BMD) loss, their clinical role remains debated, as they may mask underlying metabolic deficits and interfere with anabolic signaling.

Aim: This review evaluates mechanisms by which oral contraceptives may mask energy deficits and impact bone health in female athletes with FHA, assessing alternative pharmacological strategies.

Material and methods: A comprehensive literature search was conducted using PubMed and Web of Science for articles published between 2017 and 2026, focusing on FHA pathophysiology and metabolic outcomes of hormonal interventions.

Results: COCPs induce withdrawal bleeding without restoring HPO axis function, potentially delaying nutritional rehabilitation by masking energy deficits. Oral estrogens may downregulate hepatic IGF-1 synthesis, limiting osteoprotective efficacy. Conversely, transdermal 17- β -estradiol bypasses hepatic first-pass metabolism, preserving physiological IGF-1 levels and offering a safer profile for skeletal health.

Conclusions: COCPs should be used with caution for bone protection in FHA, prioritizing nutritional rehabilitation. Transdermal estradiol represents a physiological alternative when behavioral interventions are insufficient.

Keywords: functional hypothalamic amenorrhea, bone mineral density, oral contraceptives, low energy availability, transdermal estradiol.

1. Introduction

Functional hypothalamic amenorrhea (FHA) is one of the most common reproductive disorders, accounting for 30% to 35% of secondary amenorrhea cases in women of reproductive age and affecting an estimated 17.4 million individuals worldwide [1, 2, 3]. The syndrome is characterized by chronic hypoestrogenism, anovulation, and hypothalamic-pituitary-ovarian (HPO) axis suppression in the absence of organic etiology [1, 2]. In athletic populations, FHA is primarily driven by low energy availability (LEA), which suppresses hypothalamic pulsatile gonadotropin-releasing hormone (GnRH) secretion and leads to systemic neuroendocrine dysfunction [4, 5, 6].

The impact of FHA extends beyond reproductive failure, as the concurrent state of hypoestrogenism and impaired anabolic signaling severely disrupts skeletal homeostasis. Approximately 44% of women with FHA exhibit low bone mineral density (BMD), resulting in a 2- to 7-fold increase in fracture risk [4, 5, 7]. Emerging evidence also links prolonged hypoestrogenism and LEA to early indicators of endothelial dysfunction, potentially elevating long-term cardiovascular risk [10, 11].

Given the complexity of FHA, diagnostic differentiation from other causes of secondary amenorrhea—most notably polycystic ovary syndrome (PCOS)—represents a major clinical challenge due to overlapping clinical

and ultrasound features [12, 13, 14]. This diagnostic ambiguity often leads to therapeutic errors, including the premature and inappropriate prescription of combined oral contraceptives (COCs) [12, 13, 14]. While COCs are frequently used to manage bone mineral density loss, recent data suggest they may provide a false surrogate marker of recovery, potentially masking underlying metabolic deficits such as suppressed hepatic insulin-like growth factor 1 (IGF-1) synthesis [15, 16, 18]. Furthermore, the emergence of newer research regarding the gut-brain axis and targeted neuroendocrine modulators highlights the need for a re-evaluation of current treatment paradigms [19, 20].

Therefore, the aim of this study was to evaluate the pathophysiological mechanisms through which oral contraceptives may mask underlying energy deficits and compromise bone health, and to assess current evidence regarding alternative, more physiological pharmacological strategies in female athletes with FHA.

2. Research Materials and Methods

This narrative literature review was conducted following a systematic approach to identify relevant peer-reviewed publications and clinical practice guidelines published between 2017 and 2026. A comprehensive search was performed across the PubMed and Web of Science databases using a combination of Medical Subject Headings (MeSH) and free-text terms, including: “functional hypothalamic amenorrhea”, “low energy availability”, “bone mineral density”, “oral contraceptives”, and “transdermal estradiol”.

The inclusion criteria prioritized randomized controlled trials (RCTs), systematic reviews, meta-analyses, and clinical practice guidelines that examined the endocrine mechanisms linking low energy availability (LEA) to hypothalamic-pituitary-ovarian (HPO) axis suppression and skeletal fragility. Furthermore, studies comparing the clinical outcomes of distinct estrogen administration routes (i.e., oral versus transdermal) were specifically selected. Literature screening and selection adhered to the hierarchy of evidence-based medicine, ensuring that the included sources provided robust data on the metabolic impacts of therapeutic interventions and reflected contemporary diagnostic standards.

2.1. Study population

The studies analyzed in this review primarily comprised adolescents and women presenting with FHA, with a specific focus on individuals with a history of significant weight fluctuations, high exercise volumes, and chronic energy deficits. The selected literature encompassed both clinical and community-based cohorts, which facilitated a comprehensive assessment of diagnostic and therapeutic approaches across a broad spectrum of symptom severity and physiological adaptation.

3. Clinical Evaluation and Diagnostic Strategy

The clinical diagnostic workup for functional hypothalamic amenorrhea (FHA) necessitates high precision, as FHA remains fundamentally a diagnosis of exclusion [1, 2].

3.1. Diagnostic criteria

Clinical practice guidelines recommend initiating a diagnostic evaluation in adolescents and women whose menstrual cycle interval persistently exceeds 45 days, or who present with secondary amenorrhea for a duration of 3 months or more [1]. To ensure diagnostic safety, clinicians must first rule out pregnancy and perform a comprehensive physical and gynecological examination to exclude anatomical or organic pathologies of the reproductive tract [1, 2]. A thorough clinical history is essential, with a specific focus on weight fluctuations, dietary habits, physical activity volume, and a history of bone stress injuries [1, 10]. Furthermore, clinicians should screen for psychological stressors and maladaptive cognitive traits, such as perfectionism and cognitive rigidity, which frequently co-exist with and exacerbate HPO axis suppression [4, 8, 10].

3.2. Laboratory and ancillary evaluation

A standardized panel of baseline laboratory tests is required to assess metabolic status and exclude systemic diseases [1]. This panel should include β -human chorionic gonadotropin (β -hCG), a complete blood count, electrolytes, glucose, as well as markers of renal, liver, and inflammatory function [1]. The endocrine evaluation requires a comprehensive hormone panel to characterize the severity of HPO axis suppression and rule out alternative endocrinopathies [1]. This diagnostic profile should include serum thyroid-stimulating hormone (TSH) and free T4 (to exclude thyroid disorders), prolactin (to rule out hyperprolactinemia), as well as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are typically low or inappropriately normal in FHA [1, 2]. Quantifying serum estradiol (E₂) assists in determining the severity of hypoestrogenism, while anti-Müllerian hormone (AMH) may aid in the differentiation from polycystic ovary syndrome (PCOS) [12, 13, 14]. Furthermore, assessing total testosterone and DHEA-S is indicated if clinical signs of hyperandrogenism are present, to exclude androgen-secreting tumors or late-onset congenital adrenal hyperplasia [1, 12].

3.3. Ancillary testing and skeletal assessment

Ancillary testing should be utilized selectively based on the clinical presentation. A progestin challenge is frequently employed; FHA is typically associated with scant or no withdrawal bleeding due to chronic estrogen deficiency, whereas conditions such as PCOS generally exhibit withdrawal bleeding due to preserved estrogen exposure [1, 12, 13]. Brain magnetic resonance imaging (MRI) is indicated in cases of primary amenorrhea, persistent headaches, visual disturbances, or laboratory evidence suggesting pituitary hormone deficiency or

excess [1, 2]. Furthermore, due to the severe impact of chronic low energy availability (LEA) and hypoestrogenism on bone remodeling, obtaining a baseline bone mineral density (BMD) measurement via dual-energy X-ray absorptiometry (DXA) is recommended for any patient with 6 or more months of amenorrhea, or earlier if there is a clinical suspicion of severe nutritional deficits or established skeletal fragility [1, 4, 7].

4. Research results

4.1 Pathophysiology of skeletal fragility

Skeletal health in women with functional hypothalamic amenorrhea (FHA) is compromised through a multi-systemic cascade of endocrine and metabolic alterations initiated by chronic low energy availability (LEA) [1, 2, 4]. In adolescents and young female athletes, FHA frequently occurs during a critical developmental window, hindering the accrual of peak bone mass (PBM), which is typically finalized by the third decade of life [1, 4, 7]. This disruption of skeletal homeostasis during these formative years significantly elevates the long-term risk of osteopenia, osteoporosis, and recurrent bone stress injuries [1, 2, 4, 7].

The primary driver of skeletal fragility in FHA is chronic hypoestrogenism, which uncouples the bone remodeling process [1, 2, 4]. As estrogen is both a potent inhibitor of bone resorption and a requisite signal for osteoblast survival, its deficiency leads to unrestrained osteoclastic activity and a profound reduction in bone formation [2, 4, 8]. This persistent hypoestrogenic state disproportionately affects trabecular bone, particularly in the lumbar spine, resulting in the rapid deterioration of bone microarchitecture [2, 4, 7].

Metabolic adaptations to LEA further exacerbate this catabolic environment by inducing functional growth hormone (GH) resistance [2, 4, 8]. Despite elevated systemic GH levels in response to nutritional stress, impaired hepatic signaling pathways result in diminished circulating insulin-like growth factor 1 (IGF-1) [2, 4, 8]. Given that IGF-1 is a key stimulator of osteoblastic proliferation and collagen synthesis, its deficiency impedes adequate bone repair [2, 4]. This metabolic failure is compounded by the suppression of adipokines, such as leptin—which normally provides essential anabolic input to the skeleton—and the elevation of ghrelin, which signals energy insufficiency to the central nervous system [2, 4, 8].

Furthermore, FHA is characterized by persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hypercortisolemia [2, 8]. Elevated cortisol levels directly impair skeletal health by increasing osteoblast apoptosis and promoting osteoclastogenesis via the RANKL/OPG pathway [2, 8]. Simultaneously, cortisol negatively influences calcium homeostasis by reducing intestinal absorption and increasing renal calcium excretion [2, 8]. These catabolic processes are often accompanied by subclinical hypothyroidism, frequently manifested as low triiodothyronine (fT3) levels, which are clinically linked to reduced osteoblast activity and lower osteocalcin concentrations [2, 8]. Collectively, these neuroendocrine disturbances create a high-turnover catabolic state that renders the skeleton highly vulnerable to structural damage [1, 2, 4, 7, 10]. Beyond the skeletal implications, chronic hypoestrogenism—a hallmark of FHA—is increasingly recognized as a contributor to endothelial dysfunction, potentially increasing future cardiovascular morbidity [10, 11].

4.2 Dietary and lifestyle management

The primary objective in FHA management is the identification and reversal of the underlying energy deficit. First-line therapy involves intensive lifestyle modification aimed at restoring the energy balance required to meet the metabolic demands of the hypothalamic-pituitary-ovarian (HPO) axis [1, 7, 8, 23]. Clinical guidelines recommend achieving an energy availability (EA) threshold of at least 30–45 kcal/kg of fat-free mass (FFM) per day to facilitate the resumption of pulsatile gonadotropin-releasing hormone (GnRH) secretion [1, 7, 8, 25]. Nutritional rehabilitation, characterized by the normalization of caloric intake and the reversal of restrictive dietary patterns, is considered essential for metabolic recovery [7, 8, 25]. Current data suggest that reaching a body fat percentage of approximately 22% is frequently associated with the restoration of menstrual cyclicity [1, 8]. Furthermore, the management of exercise volume is critical; reducing high-intensity training loads is often necessary to alleviate systemic stress and improve metabolic efficiency [7, 8, 23, 24].

Emerging research indicates that the gut microbiota composition may be significantly altered in FHA, potentially contributing to the severity of neuroendocrine suppression [19]. Consequently, dietary strategies should extend beyond total caloric intake to include adequate fiber and prebiotic content, thereby supporting the gut-brain axis, which may indirectly influence HPO axis recovery and hormonal homeostasis [19].

A multidisciplinary approach, incorporating cognitive behavioral therapy (CBT), is recommended to address maladaptive attitudes toward weight, exercise, and stress, which often maintain HPO axis suppression [1, 10, 17]. CBT has been shown to reduce nocturnal cortisol secretion and increase leptin levels, thereby facilitating both ovulatory and metabolic recovery [1, 17]. In cases where these behavioral interventions fail to restore menses within 6 to 12 months, pharmacological escalation—specifically utilizing transdermal rather than oral estrogen—may be considered to preserve skeletal integrity and mitigate further bone loss [1, 4, 11].

4.3 Limitations of oral contraceptives

Although combined oral contraceptives (COCs) remain a frequently prescribed intervention for skeletal protection in women with FHA, their clinical utility is increasingly questioned by emerging evidence [1, 15, 16]. The primary limitation of COC therapy is the induction of artificial withdrawal bleeding, which functions as a false surrogate marker of endocrine recovery while failing to restore spontaneous pulsatile GnRH secretion or address the underlying energy deficit [1, 15, 16].

A critical metabolic drawback of oral estrogen administration is its impact on hepatic metabolism. Due to the hepatic first-pass effect, oral contraceptives downregulate the hepatic synthesis of insulin-like growth factor 1 (IGF-1), a vital anabolic mediator necessary for bone mineralization and osteoblast differentiation [1, 4, 22]. Consequently, recent randomized controlled trials and meta-analyses have consistently demonstrated that COCs fail to provide significant bone-protective benefits at critical cortical sites, such as the femoral neck, when compared to placebo or non-hormonal management strategies [1, 15, 16].

Furthermore, by inducing an artificial hormonal cycle, COCPs may mask underlying endocrine dysfunction. This may potentially discourage patients from pursuing the nutritional and behavioral interventions essential for reversing the state of low energy availability [1, 4, 17]. Current clinical practice guidelines advise against the routine use of COCPs solely to induce menses or improve bone mineral density (BMD) in FHA patients, emphasizing that they do not address the neuroendocrine complexity of the condition, including persistent hypercortisolemia and suppressed thyroid axis function [1, 2, 13].

4.4 Alternative pharmacotherapies

Given the limited clinical efficacy of oral contraceptive therapy, research focus has shifted toward physiological estrogen replacement and neuroendocrine modulation [1, 10, 15]. Transdermal 17- β -estradiol, administered cyclically with a progestin, is currently the preferred pharmacological strategy for bone protection in patients who do not resume menses following intensive nutritional rehabilitation [1, 15, 18]. Unlike oral preparations, transdermal administration bypasses hepatic first-pass metabolism, thereby avoiding the suppression of IGF-1 and permitting the maintenance of systemic IGF-1 levels essential for skeletal accrual [15, 16, 18]. Recent clinical data confirm that transdermal estradiol therapy is significantly more effective than COCPs in increasing lumbar spine and hip bone mineral density (BMD) in women with FHA [15, 16, 17].

Beyond skeletal protection, investigations have explored the use of low-dose estrogen as a neuroendocrine modulator to facilitate the recovery of hypothalamic-pituitary-ovarian (HPO) axis function [11]. Low-dose estrogen therapy may act as a hypothalamic "primer," assisting in the restoration of endogenous GnRH pulsatility and stabilizing the positive feedback mechanisms of the HPO axis [11]. Furthermore, recent advancements in kisspeptin research—the primary upstream regulator of GnRH secretion—have identified promising targets for pharmacological intervention [15]. Clinical studies indicate that kisspeptin receptor agonists can effectively stimulate LH and FSH secretion, offering breakthrough potential for the restoration of endogenous ovulatory function [15]. Moreover, preliminary trials assessing pulsatile GnRH therapy in women with FHA suggest that such individualized neuroendocrine approaches may optimize hormonal responses even in complex clinical phenotypes [20]. While these therapeutic strategies continue to undergo clinical validation, they represent a fundamental shift in the treatment paradigm, prioritizing the restoration of physiological HPO axis function over the administration of synthetic steroids [1, 15, 20].

5. Discussion

The management of FHA has increasingly shifted from symptomatic hormonal supplementation toward a strategy focused on the physiological restoration of the HPO axis, as advocated by recent clinical practice guidelines [1]. A critical challenge highlighted in this review is that the conventional use of COCPs for managing FHA may not align with the recovery of the hypothalamic-pituitary-ovarian axis [15, 16, 17].

The primary limitation of COCPs is that the induced withdrawal bleeding serves as a surrogate marker of endocrine status that does not reflect the reversal of low energy availability (LEA) [1, 15, 16]. This is

particularly relevant regarding skeletal health. Chronic LEA induces functional growth hormone (GH) resistance, resulting in systemic suppression of insulin-like growth factor 1 (IGF-1) [2, 4, 8]. As IGF-1 is a key mediator of osteoblast proliferation and collagen synthesis, its deficiency prevents adequate bone repair [4, 8]. Existing evidence suggests that oral estrogens, due to the hepatic first-pass effect, may further downregulate circulating IGF-1, potentially limiting the osteoprotective efficacy of COCPs at cortical bone sites [1, 15, 22]. In contrast, transdermal 17- β -estradiol bypasses hepatic metabolism and preserves IGF-1 bioavailability, suggesting a more favorable profile for bone mineral density accrual in controlled settings [15, 16, 18].

The diagnostic differentiation between FHA and PCOS also presents a significant clinical challenge, as polycystic ovarian morphology (PCOM) is frequently observed in patients with FHA [12, 13, 14]. This diagnostic overlap underscores the necessity of an individualized clinical approach that assesses the patient's metabolic status—including markers of energy balance—rather than relying solely on ovarian morphology or cycle regulation [13, 14, 15, 20].

While emerging targeted therapies—such as kisspeptin receptor agonists or pulsatile GnRH administration—represent a potentially promising evolution in managing HPO axis suppression [14, 15, 20], nutritional rehabilitation remains the established cornerstone of FHA management [1, 7, 8]. The clinical challenge remains to balance these pharmacological options with the necessity of addressing the systemic interplay between energy deficiency and skeletal fragility [1, 15, 18].

Several limitations of the current literature should be acknowledged. The heterogeneity of diagnostic criteria for FHA complicates the synthesis of clinical outcomes across studies. Furthermore, the limited duration of many clinical trials may not adequately capture the long-term interaction between LEA, hormonal interventions, and skeletal integrity, highlighting the need for further longitudinal research.

6. Conclusions

Functional hypothalamic amenorrhea (FHA) represents a complex neuroendocrine disorder and a prominent cause of secondary amenorrhea in young women. As a diagnosis of exclusion, the condition requires a comprehensive clinical and biochemical evaluation to differentiate it from organic pathologies. Skeletal fragility remains a critical long-term concern, resulting from the synergistic interaction between chronic hypoestrogenism, hypercortisolemia, and functional GH-IGF-1 resistance secondary to persistent low energy availability [2, 7, 8, 21].

Current clinical practice guidelines emphasize the restoration of energy balance as the primary management strategy [1, 7, 8, 23]. Nutritional rehabilitation and the restoration of metabolic homeostasis are fundamental for reversing the neuroendocrine suppression of the HPO axis [7, 19]. Regarding pharmacological support, evidence suggests that COCPs have limited utility for bone protection, as they do not address underlying metabolic deficits and may potentially interfere with IGF-1 signaling [1, 15, 16, 22]. In patients where behavioral interventions prove insufficient, transdermal estradiol replacement represents a more physiological approach to preserving skeletal integrity [1, 15, 18]. Future research is necessary to further validate targeted neuroendocrine therapies—such as kisspeptin receptor agonists or pulsatile GnRH administration—and to establish long-term clinical outcomes, ultimately refining the standard of care for women affected by FHA.

Author Contribution

Conceptualization, M.M.-Z.; methodology, M.M.-Z.; software, M.M.-Z.; check, M.M.-Z., J.J. and F.K.; formal analysis, J.D., Z.G. and T.K.; investigation, M.M.-Z., J.J., F.K., Z.L., M.M. and A.M.-Z.; resources, M.M.-Z.; data curation, M.M.-Z.; writing - rough preparation, M.M.-Z.; writing - review and editing, M.M.-Z., J.J., F.K., Z.G., Z.L., J.D., T.K., M.M. and A.M.-Z.; visualization, M.M.-Z.; supervision, M.M.-Z.; project administration, M.M.-Z.; receiving funding, none. All authors have read and agreed with the published version of the manuscript.

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