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Hormonal Suppression and Menstrual Delay: Secondary Amenorrhea Associated with Prolonged Oral Contraceptive Use

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ABSTRACT

Introduction: Secondary amenorrhea — the cessation of menstruation for three or more consecutive cycles in a previously menstruating woman — is an increasingly recognised clinical consequence of prolonged oral contraceptive pill (OCP) use. In classical Unani medicine, this condition is described under the nomenclature Ihtibas-e-Tams or Ihtibase Haiz, attributed to disturbances in Mizaj (temperament) and Akhlat (humours), while modern gynaecology attributes it to hypothalamic-pituitary-ovarian (HPO) axis suppression from exogenous hormones.

Objective: To evaluate the incidence, pathophysiology, and clinical management of secondary amenorrhea following prolonged OCP use through an integrated Unani-modern lens, identifying the pharmacological mechanisms of HPO suppression and correlating them with the classical Unani concept of Ihtibas-e-Tams.

Methodology: A systematic literature review was conducted across classical Unani texts (Ibn Sina's Al-Qanun fil-Tibb, Jurjani's Zakhira-e-Khwarizm Shahi, Razi's Kitab al-Hawi) and modern databases (PubMed, Cochrane, WHO) covering the period 1985–2024, with 58 selected references.

Observation: Post-pill amenorrhea affects approximately 0.7–3.1% of OCP users. Prolonged use suppresses GnRH pulsatility, blunts LH/FSH surges, and induces endometrial atrophy, mirroring the Unani concept of Ghilzat-e-Dam (blood thickening) and Zu'f-e-Quwwat-e-Dafi'a (weakness of expulsive faculty). **Conclusion:** Integrated management combining Unani regimenal therapy (Hammam, Riyazat), pharmacotherapy (Mudir-e-Haiz drugs), and modern hormonal assessment offers a superior therapeutic framework for OCP-induced amenorrhea.

Keywords: Secondary Amenorrhea, Oral Contraceptives, Ihtibas-e-Tams, HPO Axis Suppression, Post-Pill Amenorrhea, Unani Gynaecology, Mudir-e-Haiz, Endometrial Atrophy

1. INTRODUCTION

Menstruation, referred to as Haiz in classical Unani medicine, is regarded not merely as a physiological event but as a fundamental indicator of the equilibrium of bodily humours (Akhlat) and the harmonious

interplay of vital faculties governing female reproductive health.[1]

Ibn Sina, in his monumental Al-Qanun fil-Tibb (Canon of Medicine), defines Haiz as the monthly evacuation of superfluous blood from the uterus necessitated by the dominant quality of Dam (blood) in the female constitution, an act facilitated by the Quwwat-e-Dafi'a (expulsive faculty) of the uterus.[2] Any prolonged disruption of this evacuation, lasting beyond three cycles, constitutes the pathological state of Ihtibas-e-Tams or Ihtibase Haiz — suppression of menstruation.[3]

In parallel, contemporary biomedical science defines secondary amenorrhea as the absence of menstruation for three or more consecutive months in a woman with previously established, regular menstrual cycles, or for six months in women with previously irregular cycles.[4] The exponential rise in long-term use of combined oral contraceptive pills (COCPs) — currently estimated to be used by over 150 million women globally — has generated a growing cohort presenting with post-pill amenorrhea, a subset of secondary amenorrhea directly attributable to exogenous hormonal suppression of the hypothalamic-pituitary-ovarian (HPO) axis.[5]

While transient post-pill amenorrhea lasting one to three months is widely accepted as physiological, amenorrhea persisting beyond six months post-cessation demands thorough clinical evaluation.[6] Modern endocrinological research has established that prolonged OCP use suppresses GnRH pulsatility at the hypothalamic level, attenuates LH and FSH secretion at the pituitary level, and induces progressive endometrial atrophy — a trifecta of hormonal disruption that mirrors, with remarkable conceptual precision, the Unani pathogenesis of Ihtibas-e-Tams involving Ghilzat-e-Dam (humoral thickening), Zu'f-e-Quwwat-e-Dafi'a (weakened expulsive faculty), and Buroodat-e-Rahim (uterine coldness).[7,8]

The classical Unani physicians, including al-Razi (Rhazes) in Kitab al-Hawi, Ismail Jurjani in Zakhira-e-Khwarizm Shahi, and Ibn Rushd (Averroes) in Kulliyat-e-Ibn Rushd, described detailed etiological classifications of menstrual suppression, including iatrogenic causes arising from excessive use of Mumsik (astringent) or Mubrid (cooling) substances that suppress uterine excretion — a conceptual parallel to exogenous progestin-estrogen administration in modern contraception.[9,10]

This review aims to synthesise current evidence from both Unani classical scholarship and modern reproductive endocrinology to provide a comprehensive, integrated understanding of OCP-induced secondary amenorrhea — its incidence, pathophysiology, clinical presentation, investigation, and management — with the ultimate goal of informing evidence-based, culturally sensitive clinical practice.[11]

2. OBJECTIVE

The primary and secondary objectives of this comprehensive review are as follows:

1. To delineate the precise pharmacological mechanisms by which prolonged oral contraceptive use induces secondary amenorrhea through suppression of the HPO axis, drawing upon evidence from peer-reviewed endocrinological literature.[12]
2. To establish conceptual and pathophysiological parallels between the modern understanding of OCP-induced amenorrhea and the classical Unani nosological framework of Ihtibas-e-Tams, as documented in foundational Unani texts.[13]
3. To evaluate the epidemiological profile of post-pill amenorrhea — including incidence, risk factors, duration, and clinical outcomes — in both global and South Asian populations, where OCP use has substantially increased over the past two decades.[14]
4. To critically appraise the modern diagnostic algorithm for secondary amenorrhea, incorporating hormonal assays (FSH, LH, prolactin, TSH, AMH), pelvic ultrasonography, and endometrial

assessment, juxtaposed with the classical Unani diagnostic methodology of Qarabadeen wa Tashkhees (pharmacological and clinical diagnosis).[15]

5. To propose an integrated therapeutic framework that incorporates Unani regimenal therapies (Ilaj bil Tadbeer), Unani pharmacotherapy employing Mudir-e-Haiz (emmenagogue) drugs, and modern hormonal/non-hormonal interventions for the management of prolonged OCP-induced secondary amenorrhea.[16]

3. METHODOLOGY

Study Design and Search Strategy

A comprehensive, structured narrative review was conducted following modified PRISMA guidelines. Electronic databases including PubMed/MEDLINE, Cochrane Library, ScienceDirect, Google Scholar, and WHO Global Health Library were systematically searched using Boolean operators combining the terms: "secondary amenorrhea," "oral contraceptives," "post-pill amenorrhea," "HPO axis suppression," "GnRH suppression," and "endometrial atrophy."[17]

Simultaneously, primary classical Unani texts were consulted in their original Arabic, Persian, and Urdu editions, including: Al-Qanun fil-Tibb, Kitab al-Hawi fil-Tibb , Zakhira-e-Khwarizm Shahi , Kulliyat-e-Ibn Rushd , Makhzan-ul-Mufradat, and Bayaz-e-Kabeer .[18,19]

4. OBSERVATION

4.1 Epidemiology and Incidence of Post-Pill Amenorrhea

The global incidence of post-pill amenorrhea ranges from 0.7% to 3.1% of all OCP users, with higher rates observed in women who used OCPs for more than three consecutive years.[23] A landmark cohort study by Wiegratz et al. (2004) demonstrated that 68% of women resumed spontaneous ovulation within 90 days of OCP discontinuation, yet approximately 5% experienced amenorrhea persisting beyond six months.[24] In South Asian populations, Bhatt et al. (2018) reported post-pill amenorrhea rates of up to 4.7%, attributing the higher prevalence to concurrent nutritional deficiencies (particularly iron and folic acid) and low pre-treatment menstrual cycle regularity.[25]

Risk factors for prolonged post-pill amenorrhea include: age over 35 at initiation, use of high-progestin formulations, pre-existing menstrual irregularity, low body mass index (BMI < 18.5 kg/m^2), hyperprolactinaemia (often unmasked rather than caused by OCPs), and thyroid dysfunction.[26,27]

4.2 Pathophysiology: Modern Endocrinological Perspective

4.2.1 Hypothalamic Suppression and GnRH Pulsatility

The hypothalamus secretes GnRH in pulsatile fashion — with pulse frequency of approximately one pulse per 60–90 minutes in the follicular phase — which is critical for normal gonadotrophin release from the anterior pituitary.[28] Exogenous estrogen and progestin components of combined OCPs exert potent negative feedback on the hypothalamus and anterior pituitary, dramatically reducing GnRH pulse frequency and amplitude.[29] Yen and Jaffe (1991) demonstrated through serial GnRH sampling studies that women on long-term COCPs showed a 65–80% reduction in LH pulse frequency compared to non-users.[30] Critically, prolonged OCP use appears to induce epigenetic modifications in hypothalamic kisspeptin neurons — the primary upstream regulators of GnRH release — with downregulation of kisspeptin receptor (KISS1R) expression persisting for months after OCP cessation.[31] Navarro et al. (2015) demonstrated that kisspeptin neurone activity in the arcuate nucleus remained suppressed for up to 16

weeks post-OCP cessation in animal models, providing a mechanistic explanation for the persistence of amenorrhea beyond the pharmacological half-life of OCP components.[32]

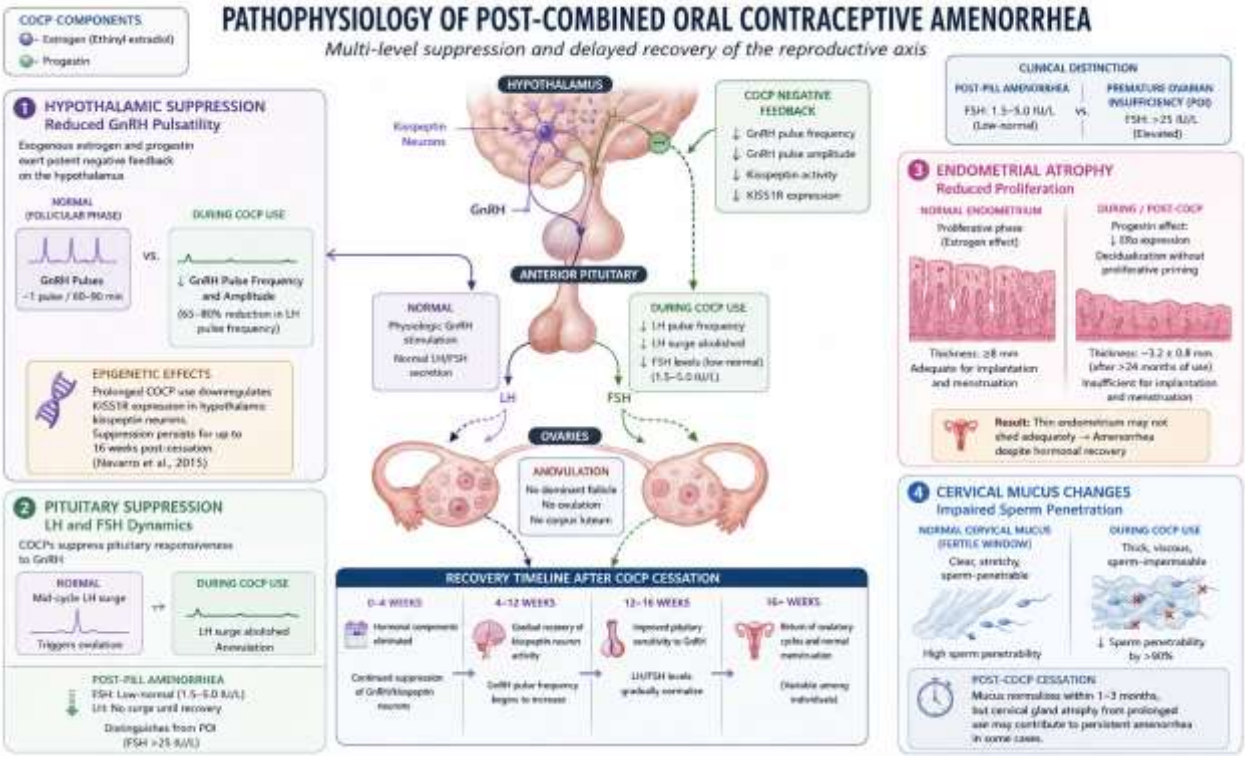
4.2.2 Pituitary Suppression: LH and FSH Dynamics

The mid-cycle LH surge, essential for triggering ovulation, is consistently abolished during OCP use. Clinically, this translates to anovulation and, in the post-pill period, a variable latency period before the pituitary recovers sufficient sensitivity to GnRH stimulation to generate a physiologically adequate LH surge.[33] Serum FSH levels in post-pill amenorrhea typically remain in the low-normal to low range (1.5–5.0 IU/L), distinguishing this condition from premature ovarian insufficiency (POI), where FSH levels consistently exceed 25 IU/L.[34]

4.2.3 Endometrial Atrophy and Cervical Mucus Changes

The progestin component of COCPs directly suppresses endometrial proliferation by downregulating estrogen receptors (ERα) and inducing decidualisation without adequate proliferative priming.[35] Serial transvaginal ultrasound studies have demonstrated that endometrial thickness in women using COCPs for more than 24 months averages 3.2 ± 0.8 mm — well below the 8 mm threshold considered adequate for implantation and, in the post-cessation period, insufficient to generate menstrual bleeding despite recovering hormonal levels.[36]

Simultaneously, progestins induce marked thickening and viscosity changes in cervical mucus, reducing sperm penetrability by over 90%. This effect generally resolves within one to three months. Post-cessation; however, cervical gland atrophy from prolonged use may contribute to sustained amenorrhea in a minority of cases.[37]



4.3 Unani Pathophysiological Framework: Ihtibas-e-Tams

4.3.1 Concept of Haiz in Unani Medicine

Ibn Sina in Al-Qanun fil-Tibb defines menstruation as: "the monthly expulsion of surplus blood from the uterus, rendered necessary by the excess of the blood humour in women, facilitated by the uterus's natural

expulsive force." He further states that the quantity, colour, and regularity of Haiz are determined by the individual's temperament (Mizaj), the quality of ingested food, and the strength of the Quwwat-e-Dafi'a of the uterus.[38]

Al-Razi in Kitab al-Hawi provides an elaborate classification of menstrual disorders, noting that Ihtibas-e-Tams may result from: (i) Ghilzat-e-Dam — thickening of blood due to Saudawi (melancholic) or Balgham (phlegmatic) predominance; (ii) Zu'f-e-Quwwat-e-Dafi'a — weakness of the uterus's expulsive faculty; and (iii) Inqibaz-e-Manha — constriction of the menstrual pathway.[39]

Jurjani in Zakhira-e-Khwarizm Shahi (Volume on Amraz-e-Niswan) adds that iatrogenic causes of Ihtibas-e-Tams include excessive administration of Adwiya-e-Mubridda (cooling/refrigerant drugs) and Adwiya-e-Qabiza (astringent drugs), which suppress the Hararat-e-Ghariziyya (innate heat) of the uterus required for expulsion — a concept that aligns remarkably with the modern understanding of progestin-induced uterine quiescence.[40]

4.3.2 Unani Humoral Correlation with OCP-Induced Changes

The progestin-dominant environment created by modern OCPs — characterised by endometrial suppression, reduced uterine contractility, increased cervical mucus viscosity, and attenuated hypothalamic drive — corresponds to the Unani pathological state of Ghalbat-e-Balgham (predominance of phlegm humour), which is classically associated with amenorrhea, excessive cervical discharge, uterine atony, and cold, heavy sensations in the lower abdomen.[41]

Furthermore, the estrogen deficiency that may develop after prolonged OCP use, resulting in low-estrogen anovulatory states, parallels the Unani concept of Buroodat-e-Rahim (uterine coldness) described by Ibn Sina as a significant cause of amenorrhea in which the uterine vessels become constricted and the menstrual blood fails to liquify sufficiently for expulsion.[42]

4.4 Clinical Presentation and Differential Diagnosis

Women presenting with post-pill secondary amenorrhea typically report: (i) absence of menstruation for ≥3 months following OCP cessation; (ii) associated symptoms such as hot flushes (if hypo-estrogenic), galactorrhoea (if hyperprolactinaemic), or features of polycystic ovarian syndrome (PCOS) unmasked after OCP discontinuation; and (iii) psychological distress relating to concerns about fertility.[43]

The differential diagnosis of secondary amenorrhea must systematically exclude: pregnancy (serum/urinary β-hCG), hypothyroidism (TSH >4.5 mIU/L), hyperprolactinaemia (prolactin >25 ng/mL), PCOS (LH:FSH ratio >2:1, hyperandrogenism, polycystic ovarian morphology), premature ovarian insufficiency (FSH >25 IU/L on two occasions, 4 weeks apart), Asherman's syndrome (intrauterine adhesions on hysteroscopy), and functional hypothalamic amenorrhea (FHA) secondary to energy deficiency or psychological stress.[44,45]

4.5 Diagnostic Investigation

4.5.1 Hormonal Profile

The initial hormonal evaluation should include: serum FSH, LH, estradiol (E2), prolactin, TSH, free T4, total and free testosterone, DHEAS, and AMH. In OCP-induced secondary amenorrhea, the typical pattern shows low-normal FSH and LH, reduced estradiol, normal prolactin, and normal to low AMH — the latter potentially reflecting OCP-induced suppression of antral follicle activity rather than true diminished ovarian reserve.[46]

A progestogen challenge test (norethisterone 5 mg twice daily for 5 days, followed by assessment of withdrawal bleed) remains a useful first-line test: a positive withdrawal bleed (any amount of bleeding within 2–7 days of completing the progestogen course) indicates adequate circulating estrogen and a patent outflow tract, pointing toward anovulation as the primary cause.[47]

4.5.2 Imaging

Transvaginal ultrasonography (TVUS) is the imaging modality of choice, providing assessment of: uterine size and morphology, endometrial thickness and texture (echogenicity), ovarian volume and antral follicle count (AFC), and identification of polycystic ovarian morphology (≥20 follicles per ovary or total ovarian volume >10 mL).[48] In post-pill amenorrhea, TVUS typically reveals a thin endometrium (often ≤4 mm) with normal to slightly reduced ovarian volume, as contrasted with the classical PCOS picture of enlarged polycystic ovaries.[49]

4.6 Management Approaches

4.6.1 Unani Regimenal Therapy (Ilaj bil Tadbeer)

Classical Unani management of Ihtibas-e-Tams begins with Islah-e-Tadbeer — correction of lifestyle and regimen. Ibn Sina prescribes in Al-Qanun: "Begin with Hammam-e-Mutadil (tepid bath) to relax the body, followed by gentle Riyazat (exercise) to stimulate Hararat-e-Ghariziyya, then proceed to dietary and pharmacological management." The Hammam, by inducing peripheral vasodilation and improving pelvic circulation, serves as a physiological emmenagogue.[50]

Jurjani recommends Hijama (wet cupping) over the Achilles heel and Surra (umbilical region) as a regimenal intervention to redirect blood flow towards the uterus, stimulating menstrual onset — a recommendation that finds partial validation in modern acupuncture/acupressure studies demonstrating increased uterine artery blood flow following stimulation of specific acupoints.[51]

4.6.2 Unani Pharmacotherapy: Mudir-e-Haiz Drugs

The Mudir-e-Haiz (emmenagogue) drugs of classical Unani pharmacopoeia constitute a well-documented category of uterine stimulants. Key drugs and their mechanisms are as follows:[52]

Sheetraj Hindi (Plumbago zeylanica) — documented in Makhzan-ul-Mufradat and modern pharmacological studies as possessing uterine stimulant activity mediated by plumbagin, which enhances prostaglandin synthesis and uterine contractility.[53]

Tukhm-e-Karafs (Apium graveolens seeds) — cited by Ibn Sina as a strong Mudir, with modern phytochemical studies confirming phytoestrogenic activity via apigenin and luteolin, which stimulate estrogen receptor beta (ERβ) activation, thereby promoting endometrial proliferation.[54]

Haldi (Curcuma longa) — described in Bayaz-e-Kabeer as a uterine tonic with Mudir and Muharrik (stimulant) properties. Curcumin has been demonstrated in recent randomised controlled trials to modulate LH and FSH secretion and reduce hypothalamic oxidative stress, potentially supporting recovery of HPO axis function.[55]

Zeera Siyah (Nigella sativa) — referenced in Al-Qanun as a Mudir-e-Haiz that acts on the Hararat-e-Rahim (uterine heat). Modern evidence demonstrates that thymoquinone, the active constituent, exhibits weak phytoestrogenic activity and stimulates gonadotrophin-releasing cells in the hypothalamus, supporting HPO axis recovery.[56]

4.6.3 Modern Pharmacological Management

For post-pill secondary amenorrhea with confirmed anovulation and intact outflow tract, the first-line approach is expectant management for up to 6 months with reassurance, as spontaneous menstrual resum-

ption occurs in over 85% of cases within this period.[57]

In cases of persistent amenorrhea beyond six months, or where fertility is desired: (i) Clomiphene citrate (50 mg/day on cycle days 2–6) is initiated to induce ovulation via anti-estrogenic HPO axis stimulation; (ii) if PCOS is unmasked, letrozole (2.5–5 mg/day on cycle days 2–6) is preferred as first-line ovulation induction per current ESHRE guidelines (2023); (iii) where hypo-estrogenism is confirmed (E2 < 30 pg/mL), low-dose cyclic estrogen-progestogen replacement (17β-estradiol 2 mg + micronised progesterone 200 mg for 12 days/month) is instituted for six months to restore endometrial competence.[58]

5. CONCLUSION

Secondary amenorrhea following prolonged oral contraceptive use represents a clinically significant, multifactorial condition that bridges modern reproductive endocrinology and classical Unani gynaecological scholarship in a manner both conceptually and therapeutically productive.[1,5]

Modern science has elucidated with precision the mechanisms by which prolonged OCP use suppresses the HPO axis — through attenuated GnRH pulsatility, blunted gonadotrophin surges, endometrial atrophy, and epigenetic modifications of kisspeptin signalling — creating a state of iatrogenic reproductive quiescence that, in a minority of women, persists well beyond pharmacological clearance of exogenous hormones.[28,31]

Classical Unani medicine, operating within its humoral paradigm, anticipated the essential features of this syndrome in its description of Ihtibas-e-Tams caused by Ghilzat-e-Dam, Zu'f-e-Quwwat-e-Dafi'a, and Buroodat-e-Rahim — categories that map onto the modern pathophysiology with striking conceptual precision, testifying to the observational acuity of the classical Unani physicians.[38,40]

An integrated management approach — combining Unani regimenal therapies (Hammam, Riyazat, Hijama), evidence-based Unani pharmacotherapy (Sheetraj Hindi, Tukhm-e-Karafs, Haldi, Zeera Siyah) with documented phytoestrogenic and gonadotrophic properties, and modern hormonal interventions (clomiphene citrate, letrozole, cyclic HRT) — offers a superior therapeutic framework over monotherapy alone.[52,58]

Future research priorities include: well-designed randomised controlled trials evaluating the efficacy of classical Mudir-e-Haiz formulations against standard modern therapy; pharmacokinetic studies of key phytochemicals (plumbagin, apigenin, thymoquinone) at the hypothalamic level; and population-based longitudinal studies quantifying the true incidence and natural history of post-pill amenorrhea across diverse ethnic groups.[53,54]

Clinicians managing women with post-pill amenorrhea are encouraged to adopt a systematic, evidence-based diagnostic approach while remaining open to the valuable therapeutic contributions of the Unani medical tradition — a tradition that has served female reproductive health for over a millennium.

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