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Leading Article

Secondary Amenorrhoea Related to Neuro-Endocrinological Causes

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Abstract

Objective: To review the neuro-endocrinological causes of secondary amenorrhoea, focusing on its pathophysiology, mediators, and management strategies.

Design: A comprehensive review of current evidence on physiological, pathological, and iatrogenic causes of secondary amenorrhoea, emphasizing functional hypothalamic amenorrhoea (FHA), hyperprolactinemia, and pituitary-related disorders.

Method: The review integrates findings from experimental studies, clinical observations, and expert consensus to outline the mechanisms underlying hypothalamic-pituitary-ovarian (HPO) axis dysregulation. Key mediators, including leptin, insulin, and fibroblast growth factor-21 (FGF-21), are explored, alongside conditions such as Sheehan's syndrome, sellar lesions, and genetic mutations.

Results: Secondary amenorrhoea affects 3–4% of women globally, with over half of cases linked to HPO axis dysfunction. FHA emerges as a leading cause, driven by stressors such as malnutrition and chronic illness. Hyperprolactinemia, both physiological and pathological, significantly impacts gonadotropin secretion and ovarian function. Pathological conditions, including pituitary adenomas, hypothyroidism, and infiltrative diseases, further contribute to amenorrhoea. Iatrogenic factors, such as cranial irradiation and medication use, also play a role. Early diagnosis and targeted interventions, including hormone replacement therapy and addressing reversible causes, are crucial for restoring gonadotropin function and improving fertility outcomes.

Conclusion: Secondary amenorrhoea is a multifaceted condition often resulting from neuro-endocrinological disturbances. A multidisciplinary approach is essential to accurately diagnose and manage the condition, ensuring optimal reproductive and overall health outcomes.

Introduction

Amenorrhoea refers to the absence of menstrual bleeding. It is a normal physiological state in pre-pubertal girls, pregnant women, those exclusively breastfeeding, and postmenopausal women. In women of reproductive age, the most common cause of amenorrhoea is undiagnosed pregnancy. When pregnancy is excluded, diagnosing the underlying cause can be challenging.[12]

Secondary amenorrhoea is clinically significant when it meets the following criteria[3]:

- Normal pubertal milestones are present.
- Menarche has been attained.
- Absence of menstruation for at least three or six months in irregular cycles.

Globally, secondary amenorrhoea affects approximately 3–4% of women.[4] Over 50% of cases are associated with dysfunction or dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis.[5] This article focuses on neuro-endocrinological causes of secondary amenorrhoea, many of which are associated with coexisting fertility issues. For clarity, the etiological causes are categorized as outlined in Table 1.

Table-1; Neuro-endocrinological causes of secondary amenorrhoea

Physiological	**Pathological**	**Iatrogenic**
Functional hypothalamic amenorrhoea	Hyperprolactinemia	Pituitary surgery
Hyperprolactinemia due to pregnancy/lactation	Sellar mass/lesions	Cranial irradiation
	Sheehan's syndrome	Medication induced
	Infective or infiltrative diseases	*a. GnRH Suppression*
	Brain trauma	*b. Hyperprolactinemia*
	Adrenal pathology	*c. Hypophysitis*
	Genetic causes	

Table-2; Mediators for functional hypothalamic amenorrhoea

Leptin	A mediator of functional amenorrhoea. Secreted by adipocytes and low in FHA. Low levels associated with reduced GnRH and anovulation via Kisspeptin mediated pathway. Adequate fat stores are essential for Leptin production and is probably the basis when extreme fat loss related to FHA[10].
Insulin	Insulin has been shown to modulate the HPO axis. In obese, excess insulin with resistance creates functional hypoinsulinemia. Whereas in very thin individuals (under nutrition), there is actual hypoinsulinemia. When insulin and its receptor signaling is not properly regulated, LH level reduces and anovulation occurs[11].
FGF-21	Role in humans is unknown. But this liver derived factor is up regulated in starvation and associated with low LH and anovulation via interruption to Kisspeptin, a potent stimulator of GnRH secretion[12].

(A) Physiological Secondary Amenorrhoea

(1) Functional Hypothalamic Amenorrhoea (FHA)

Functional hypothalamic amenorrhoea (FHA), also known as stress-induced amenorrhoea, is one of the most common causes of secondary amenorrhoea. It occurs in conditions such as severe malnutrition, emotional stress, extreme physical exercise, and chronic illness. In response to these stressors, the body prioritizes essential survival mechanisms over reproductive functions, redirecting energy and resources away from the reproductive system.

The hypothalamic-pituitary-adrenal (HPA) axis becomes inactivated during periods of stress, suppressing the HPO axis. Corticotropin-releasing hormone (CRH), produced by the hypothalamus, plays a dominant role by inhibiting gonadotropin-releasing hormone (GnRH) secretion. This results in reduced pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Experimental studies have demonstrated that this effect can be reversed by external administration of GnRH, highlighting its therapeutic potential in such cases.

Additionally, elevated CRH levels stimulate adrenocorticotropic hormone (ACTH) secretion from the pituitary, which independently impairs reproductive function, irrespective of adrenal steroid production.[67] Supraphysiological levels of glucocorticoids are also known to suppress LH responses to GnRH and reduce the effects of estradiol on the uterus.[89]

(2) Physiological Hyperprolactinemia (Table-3)

Hyperprolactinemia is the most common cause of pituitary-associated amenorrhea. These women have reduced LH pulse frequency and reduced LH responsiveness to estrogen, suggesting that GnRH suppression may be a key factor. This is supported by the fact that in hyperprolactinemic amenorrhea women, treatment with pulsatile GnRH results in follicular maturation and ovulation when coupled with a human chorionic gonadotropin trigger. In vitro studies have found that prolactin has a direct inhibitory role on ovarian granulosa cells and thereby directly disrupts ovarian function13,14.

Although most women with hyperprolactinemia have amenorrhea, some have ovulatory menstrual cycles. They do suffer from infertility due to short luteal phase defects15. Therefore, treating hyperprolactinemia may be important even in regularly menstruating women.

A number of physiological causes of hyperprolactinemia and amenorrhea, including pregnancy, do not warrant treatment and, therefore, should be excluded before initiation of treatment.

Table-3; physiological causes of hyperprolactinemia

Pregnancy	Pregnancy is the most common cause of Hyperprolactinemia. Prolactin levels increase during pregnancy and peak at delivery. In women who do not breast feed, prolactin levels usually decrease during the first 72 hours postpartum and normalize by 3 weeks[16,17].
Lactation	Suckling increases prolactin levels, although this usually subsides by 12 weeks due to the postpartum drop in estradiol levels resulting in decreased lactotroph hyperplasia. Similar to prolactin-induced amenorrhea, lactational amenorrhea is associated with reduced LH-pulse amplitude and frequency and reduced LH responsiveness to estrogen[18,19].
Macro-prolactinemia	Predominate prolactin form is 23kD in humans. There is another higher molecular mass form called macroprolactin. It is slowly cleared from circulation and this complex mass is less bioactive plus cause no symptoms. But Hyperprolactinemia that results from macro molecule is evident in ¼ Hyperprolactinemia individuals and they are prone for amenorrhoea[20].

(B) Pathological Secondary Amenorrhoea

(1) Pathological Hyperprolactinemia

Pathological hyperprolactinemia commonly results in amenorrhoea with or without subfertility. Elevated prolactin levels in these cases warrant thorough evaluation. The causes are summarized in Table 4.

Causes of Pathological Hyperprolactinemia

1. Lactotroph Adenoma

Lactotroph adenomas are the most common type of pituitary adenoma that secrete prolactin, making them the leading cause of pathological hyperprolactinemia. The size of the adenoma correlates with serum prolactin levels. These benign lesions cause amenorrhoea through mechanisms similar to those described for physiological hyperprolactinemia.[21]

2. Stalk Disruption

Dopamine, secreted by the arcuate nucleus, exerts tonic inhibition on prolactin secretion. Disruption of the pituitary stalk, which connects the hypothalamus and pituitary, reduces dopamine-mediated inhibition, leading to hyperprolactinemia. Stalk disruption can result from cranial trauma or large seller masses.

3. Primary Hypothyroidism

Thyrotropin-releasing hormone (TRH) stimulates the secretion of both thyroid-stimulating hormone (TSH) and prolactin. Chronic elevation of TRH in primary hypothyroidism leads to hyperprolactinemia, which is reversible with thyroxine replacement therapy.[22,23]

4. Chronic Renal Failure (CRF)

CRF is associated with increased prolactin secretion due to reduced lactotroph responsiveness to dopamine suppression and impaired clearance of prolactin.

However, it is an uncommon cause of secondary amenorrhoea in women.

5. Chest Wall Injury

Chest wall injuries can rarely cause hyperprolactinemia and amenorrhoea. Neurogenic stimulation at the site of injury is believed to be responsible for this effect.[24]

(2) Sellar Mass/Lesions (e.g., Non-Lactotroph Adenomas)

Lesions larger than 1 cm can compress pituitary gonadotrophs or disrupt the stalk, leading to hyperprolactinemia. These include functional or non-functional adenomas, craniopharyngiomas, Rathke's pouch cysts, vascular lesions, or other solid tumors.

(a) Cushing's Disease

Amenorrhoea is a common feature of adrenocorticotropic hormone (ACTH)-secreting adenomas. Up to one-third of affected women experience menstrual irregularities. These patients have markedly elevated serum cortisol levels, reduced serum estradiol, and lower sex hormone-binding globulin (SHBG) levels. Despite elevated adrenal androgens, the amenorrhoea in Cushing's disease is primarily due to GnRH suppression caused by high cortisol concentrations rather than androgen excess.[25]

(b) Acromegaly

Growth hormone (GH) secreting adenomas can cause amenorrhoea and subfertility. These women typically exhibit low LH and estradiol levels, contributing to menstrual irregularities.[26]

(c) Thyrotrophic Adenomas

Thyrotropin (TSH)-secreting tumors are associated with thyrotoxicosis. These tumors can cause elevated SHBG, FSH, LH, and estradiol levels. However, the absence of a mid-cycle LH surge, as seen in physiological cycles, results in anovulation and amenorrhoea in some women.[27]

(d) Infiltrative Conditions

Infective, inflammatory, or malignant infiltrations of the hypothalamic-pituitary axis can induce amenorrhoea. Most cases are secondary to primary breast or lung malignancies.[28]

Examples include:

- Hypophysitis
- Tuberculosis
- Sarcoidosis
- Hemochromatosis

(e) Sheehan's Syndrome

During pregnancy, the pituitary gland enlarges due to estrogen-induced hypertrophy of lactotroph cells. This can compress the pituitary vascular supply. Significant blood loss during pregnancy (e.g., major postpartum hemorrhage) can reduce pituitary perfusion, leading to ischemic necrosis.[29]

Patients with Sheehan's syndrome develop hypopituitarism, manifesting as reduced breast milk production and amenorrhoea. Studies indicate delays in the diagnosis of this condition. Improved labor management protocols aimed at minimizing postpartum hemorrhage have significantly reduced cases of pituitary necrosis secondary to obstetric bleeding.[30]

(f) Cranial Trauma

Traumatic brain injuries and subarachnoid hemorrhages are known to cause hypogonadism and subsequent amenorrhoea.

(g) Adrenal Tumors

Glucocorticoid- and androgen-secreting adrenal tumors can cause amenorrhoea. Excess cortisol suppresses GnRH secretion, while elevated androgens inhibit LH pulse frequency.[31]

(h) Genetic Causes

Several genetic disorders can cause amenorrhoea, often with distinct phenotypic manifestations affecting the hypothalamic-pituitary-adrenal (HPA) or hypothalamic-pituitary-ovarian (HPO) axis. Examples include:

- KAL-1 Gene Mutation: Associated with Kallmann syndrome, an anosmic variant of idiopathic hypogonadotropic hypogonadism.
- KISS1/KISS1R Mutation: Causes idiopathic hypogonadotropic hypogonadism with normal olfactory function (normosmia).

(i) Iatrogenic Causes

Several medical interventions can result in amenorrhoea, including:

- Medication-Induced Amenorrhoea:

GnRH agonists, GnRH antagonists, and opioid use can suppress GnRH secretion or cause hyperprolactinemia. Opioid-induced hypogonadism is primarily mediated by GnRH inhibition. Immunotherapy agents like ipilimumab can induce hypophysitis and subsequent pituitary failure, leading to amenorrhoea.

- Radiation-Induced Hypopituitarism
- Post-Pituitary Surgery

Conclusion

Secondary amenorrhoea often arises from complex neuro-endocrinological disturbances. Evaluation and management require a multidisciplinary approach due to the intricate pathophysiology. Hormone replacement therapy remains a cornerstone of care for addressing vasomotor symptoms and preventing osteoporosis. However, identifying and treating reversible causes is essential to restore gonadotropin function and improve outcomes.

Conflicts of Interest: None

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