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REVIEW ARTICLE

Neuroendocrine Contributions to Polycystic Ovary Syndrome (PCOS)

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# Neuroendocrine drivers of polyendocrine metabolic ovarian syndrome (PMOS) and the modifying role of adiposity

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## Abstract

Polyendocrine metabolic ovarian syndrome (PMOS), previously known as polycystic ovary syndrome (PCOS), is the commonest cause of anovulatory subfertility and represents a substantial and growing healthcare burden. PMOS is a complex neuroendocrine-ovarian-metabolic disorder in which dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis disrupts ovarian function, further exacerbated by associated metabolic dysfunction. This review synthesises the current clinical evidence on neuroendocrine dysfunction in PMOS, using luteinising hormone (LH) pulsatility as a surrogate marker of gonadotrophin-releasing hormone (GnRH) neuronal activity. By drawing on parallel evidence from women with and without PMOS, we examine how adiposity modulates these parameters. In women without PMOS, obesity is associated with hypothalamic suppression. By contrast, a key neuroendocrine feature of PMOS is accelerated hypothalamic pulsatile GnRH neuronal activity, which preferentially drives LH secretion, culminating in ovarian androgen excess, follicular arrest, and anovulation. Although obesity is associated with lower mean LH concentrations due to attenuation of LH pulse amplitude, pulse frequency remains heightened. Given the high prevalence of obesity in PMOS, dampening of raised LH concentrations with obesity challenges its use as part of diagnostic criteria for PMOS in populations where obesity is prevalent. Obesity-induced metabolic dysfunction also leads to hyperinsulinaemia, which further exacerbates ovarian hyperandrogenism. The interplay between metabolic dysfunction and reproductive health is illustrated by weight-management interventions, which consistently improve ovulatory function in women with obesity and PMOS. Understanding the neuroendocrine impact of obesity on the pathophysiology of PMOS can inform both diagnostic accuracy and therapeutic targets.

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GnRH pulsatility, LH pulsatility, obesity, PCOS, PMOS

## 1 | INTRODUCTION

Polyendocrine metabolic ovarian syndrome (PMOS), previously known as polycystic ovary syndrome (PCOS), is the most common cause of anovulatory subfertility in reproductive-aged women, with an estimated global prevalence of 12.1% using the modified Rotterdam criteria.[1] Over the past two decades, its incidence in the UK has nearly doubled from 1.22 to 2.20 per 1000 person-years, while its point prevalence has more than tripled from 1.02% to 3.48%, paralleling rising metabolic disease burden and imposing substantial healthcare and societal costs.[2] PMOS was also 2–3-fold more common in ethnic minority groups.[2] Nevertheless, the lower prevalence compared to global estimates suggests that PMOS is significantly under-recognised and under-diagnosed.

The diagnostic criteria for PMOS, as defined by the 2003 Rotterdam criteria, and subsequently updated in the 2018 and 2023 international PMOS guidelines, require the presence of clinical and/or biochemical hyperandrogenism, oligo-anovulation, and sonographic features of polycystic ovarian morphology (PCOM), following exclusion of alternative diagnoses.[3] The 2023 international guidelines also recognised anti-Müllerian hormone (AMH), a dimeric glycoprotein that correlates with antral follicle count (AFC), as a surrogate marker for PCOM in adults, allowing its use instead of ultrasound in the diagnosis of PMOS.[4]

PMOS is a complex metabolic-reproductive disorder arising from dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis in concert with intrinsic ovarian dysfunction and metabolic stress.[5] The key neuroendocrine abnormality in PMOS is accelerated pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. This shift towards higher GnRH pulse frequency is sensed by gonadotrophs and preferentially drives luteinising hormone (LH) synthesis over follicle-stimulating hormone (FSH), resulting in LH excess and establishing a hormonal environment conducive to follicular arrest and hyperandrogenism.[6–10] Hyperandrogenism, in turn, impairs progesterone-mediated negative feedback by diminishing hypothalamic sensitivity to sex-steroid restraint,[11] leading to heightened excitability of the arcuate kisspeptin-neurokinin B-dynorphin (KNDy) neurons, now recognised as the GnRH pulse generator, thereby further perpetuating increased GnRH pulse activity.

Obesity introduces a mechanistically distinct dimension to this axis. Chronically increased leptin concentrations from increased adiposity can result in leptin resistance, simulating low leptin states. Because leptin provides a permissive signal for hypothalamic neuroendocrine activity, reduced leptin signalling can impair hypothalamic reproductive function. At the level of the pituitary gland, obesity-associated systemic inflammation and insulin resistance also attenuate pituitary responsiveness to GnRH.[12,13] These mechanisms, in association with increased renal clearance of endogenous LH due to changes in the form of LH with increasing body mass index (BMI), result in blunted LH pulse amplitude and reduced LH concentrations.[12,14] Thus, when obesity coexists with PMOS, these opposing neuroendocrine alterations may obscure the raised LH concentrations expected in PMOS without obesity.[12] Moreover, obesity amplifies metabolic dysfunction. Insulin resistance promotes hyperinsulinaemia, which acts with LH at the ovary and amplifies intrafollicular androgen production, worsening metabolic dysfunction.[6,15] This review synthesises current evidence on GnRH and LH pulsatility in PMOS and examines how obesity modifies these neuroendocrine dynamics.

## 2 | PHYSIOLOGY OF GnRH AND LH PULSATILITY

The reproductive axis is organised around a temporally programmed GnRH signal generated by specialised hypothalamic circuits. GnRH neurons, located within the medial preoptic area (POA) (equivalent to the rostral periventricular area of the third ventricle (RP3V) in non-primates) and the infundibular nucleus (equivalent to the arcuate nucleus (ARC) in non-primates), project to the median eminence where they release GnRH into the hypophyseal portal system (Figure 1).[16,17] Pituitary gonadotrophs decode this signal and selectively regulate LHβ and FSHβ transcription.[18,19] The temporal characteristics of GnRH release determine gonadotroph output and, by extension, ovarian steroidogenesis and follicular development.

Pulsatile GnRH secretion is indispensable for gonadotroph responsiveness. In seminal primate experiments, hypothalamic radiofrequency ablation eliminated endogenous GnRH secretion, and only pulsatile, but not continuous, GnRH administration restored LH and FSH release.[20]

The origin of pulsatility is now attributed to a hypothalamic pulse generator within the mediobasal hypothalamus.[21,22] Isolation of the mediobasal hypothalamus preserves LH pulsatility while eliminating LH surge capacity, which is thought to originate from kisspeptin-mediated stimulation of GnRH neuronal somata within the POA/RP3V.[22,23]

The pulse generator is now recognised as the population of ARC neurons co-expressing kisspeptin, neurokinin B (NKB) and dynorphin, the KNDy neurons. These neurons form an interconnected excitatory-inhibitory circuit capable of generating rhythmic pulses. While KNDy neurons do not express the kisspeptin receptor (KISS1R), they do express the NKB receptor (NK3R) and κ-opioid receptor (KOR).[24,25] NKB and NK3R agonists provide excitatory inputs whilst dynorphin/KOR agonists impose inhibitory constraints. The regulation of KNDy neurons therefore occurs in an autocrine/paracrine manner, with stimulatory NKB and inhibitory dynorphin signalling, whilst kisspeptin acts on downstream GnRH neurons as the final excitatory

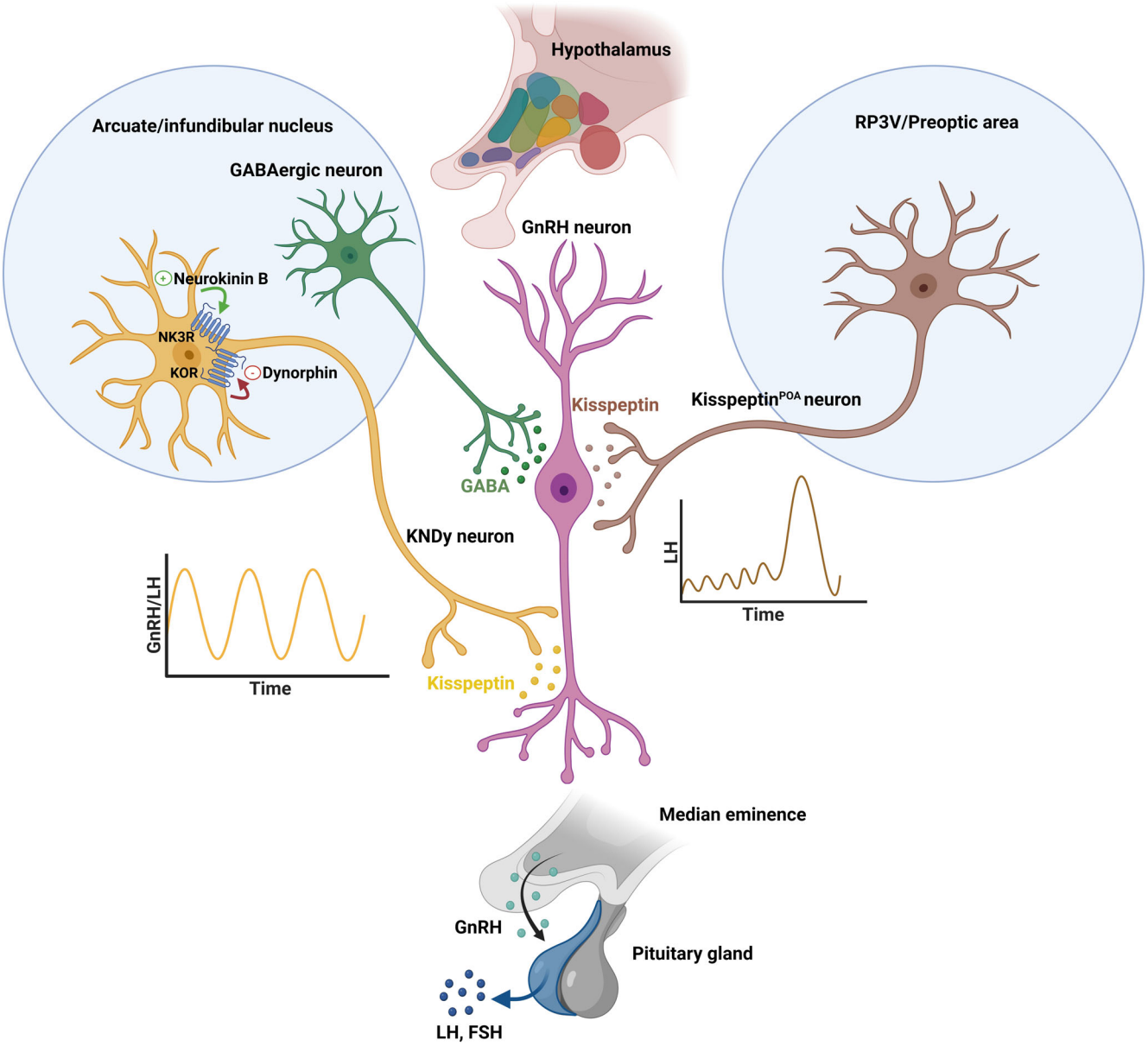



**FIGURE 1** Overview of the central neuroendocrine regulation of the hypothalamic–pituitary–ovarian axis in females. Kisspeptin is released from the preoptic area (POA) (rostral periventricular area of the third ventricle (RP3V) in non-humans) and infundibular nucleus (arcuate nucleus in non-humans) of the hypothalamus. The kisspeptin neurons in the arcuate/infundibular nucleus co-express neurokinin B and dynorphin, collectively known as the KNDy neuron, which is involved in autocrine/paracrine regulation of tonic pulsatile kisspeptin secretion, acting via the neurokinin B (NKB/NK3R) and κ-opioid (KOR) receptors respectively. Kisspeptin release is stimulated by neurokinin B and inhibited by dynorphin. Kisspeptin secretion from the arcuate/infundibular nucleus promotes the pulsatile release of GnRH from hypothalamic GnRH neurons in the median eminence. These subsequently promote secretion of anterior pituitary gonadotrophin hormones (LH and FSH). The kisspeptin neurons in the POA/RP3V primarily stimulate the GnRH neurons in the POA/RP3V to promote the mid-cycle LH surge. GABAergic neurons in the arcuate nucleus also form excitatory synapses with GnRH neuronal cell bodies and proximal dendrites, promoting GnRH release.

output from KNDy neurons[22,26] (Figure 1). In support of this, double-label immunohistochemical analysis of kisspeptin-immunoreactive neurons in the ARC of ovariectomised goats revealed extensive co-localisation: 99.5% of kisspeptin-immunoreactive neurons also expressed NKB, and 78% co-expressed dynorphin.[27] Triple-labelling further confirmed kisspeptin-NKB-dynorphin co-expression within these ARC neurons whereas many kisspeptin-containing fibres co-expressing NKB or dynorphin were also visualised to project to the external zone of the median eminence, where kisspeptin neurons were previously shown to lie in close apposition to GnRH neurons.[27,28] Electrophysiological recordings in the ARC identified periodic multiunit electrical activity (MUA) volleys that tightly coincided with LH pulses and were stimulated by NKB but dose-dependently suppressed by dynorphin.[27] Similarly, immunohistochemical analysis of human post-mortem samples identified ~77% of kisspeptin-54 immunoreactive neuronal somata in the infundibular

nucleus also exhibiting preproneurokinin B immunoreactivity while ~95% of the preproneurokinin B-immunoreactive somata co-expressed kisspeptin-54.[29] The above reinforces the dogma of an autostimulatory KNDy network acting on GnRH neurons to provide pacing signals, generating and maintaining pulsatile GnRH secretion.

LH pulsatility is widely accepted as a surrogate marker for GnRH activity.[30] Early work by Santen & Bardin quantified follicular-phase LH pulses in 5 healthy eugonadal women with regular cycles at ~3.2 ± 0.36 spikes per 6 h (day 8 of the cycle), with luteal-phase pulses halving to ~1.6 ± 0.24 spikes per 6 h (day 22 of the cycle).[31]

Pulsatile LH secretion patterns vary according to different phases of the menstrual cycle as sex-steroid feedback imposes phase-specific modulation of the pulse generator. During the follicular phase, oestradiol concentrations exert negative feedback in the arcuate/infundibular nucleus via non-classical oestrogen receptor alpha (ERα) signalling that suppresses *Kiss1* and *NKB* expression.[32,33] In the luteal phase, progesterone slows pulse frequency, an effect likely facilitated by prior oestradiol-induced upregulation of progesterone receptors (PGRs) in the ARC.[34] Progesterone enhances dynorphin tone, extending the inter-pulse interval and suppressing GnRH output.[35] Progesterone also acts on pituitary gonadotrophs to flatten the response to GnRH stimulation via suppression of GnRH-induced LHβ transcription.[36] Androgens modulate hypothalamic sensitivity to steroid feedback and KNDy neurons express androgen receptors (ARs) to mediate the negative androgen feedback on GnRH neurons.[37,38] Beyond steroid feedback, the KNDy neurons integrate metabolic cues including leptin and insulin to enable reproductive function to match the individual's broader physiological context. Collectively, this framework provides the baseline against which the disordered pulsatility of PMOS and its modulation by BMI can be understood.

## 3 | ALTERED LH PULSATILITY IN PMOS

PMOS is characterised by persistently elevated GnRH pulse frequency, with disrupted cycle-phase modulation. Accelerated GnRH pulse frequency preferentially upregulates LHβ over FSHβ transcription, favouring LH dominance.[39] The resulting elevation in LH/FSH ratio promotes ovarian androgen excess and contributes to follicular arrest.[8–10,40]

Mechanistic support for this model comes from prenatally androgenised (PNA) female rhesus monkeys, which recapitulate key neuroendocrine features of human PMOS.[41] In these animals, LH pulse frequency is increased by ~120% relative to controls.[42] Human studies consistently replicate these findings, with raised LH pulse frequency observed across multiple PMOS cohorts.[43,44] Quantification of LH pulse frequency over 24 h demonstrated frequencies of ~22 pulses in lean PMOS and ~24 pulses in obese PMOS, compared with ~16 pulses in BMI-matched controls, representing a relative increase of ~38% and ~50% respectively.[45] Elevated basal LH concentrations accompany these changes, with 47% of women with PMOS exhibiting LH concentrations above the 95th percentile of reference populations.[46]

Impaired sex-steroid mediated feedback leads to altered LH pulsatility in PMOS. In PNA monkeys, intramuscular administration of PGR antagonist, replicating the removal of progesterone-mediated inhibition, resulted in a blunted LH rise with 25% of LH values exceeding baseline, compared to 83% in control animals, indicating centrally-impaired progesterone-mediated negative feedback.[42] In support of this, ovariectomy in PNA mice resulted in only a blunted LH rise compared to dioestrus controls, and lack of LH suppression following oestradiol supplementation.[47] Interestingly, some studies failed to show a difference in basal LH levels between control and PNA mice, as would be expected in constitutionally impaired sex-steroid-mediated feedback.[47,48] Instead, the pathology becomes more prominent at either extremes; after exogenous sex-steroid administration or following ovariectomy with elimination of the baseline sex-steroid milieu.[47,48] Similarly, Pastor and colleagues demonstrated that while women with PMOS did suppress their LH pulse frequency in response to progesterone exposure, higher concentrations were required to mediate this suppression, which was of smaller calibre compared to controls.[49]

PGRs are expressed on KNDy neurons and progesterone suppresses *Kiss1* mRNA, while upregulating dynorphin (*Pdyn*) mRNA expression in the ovine ARC.[50,51] However, direct KNDy-mediated progesterone negative feedback is disputed. Recently, selective deletion of PGRs from kisspeptin neurons in mice (KPRKO mice) did not alter LH pulsatility in dioestrus or oestrus, nor the ability of exogenous progesterone to blunt an LH rise, and had no effect on kisspeptin or dynorphin expression.[52] Thus, progesterone-mediated negative feedback might instead be conveyed via a separate neuronal population feeding into the KNDy network.[52] However, this deletion was not complete (11.5% ± 2.2% residual PGR mRNA expression in KPRKO mice), and it is plausible that it reflects circuit redundancy.[52] Further work localising functional PGRs within this network is warranted.

## 4 | INSIGHTS FROM GnRH STIMULATION AND CENTRAL MANIPULATIONS

GnRH stimulation tests have demonstrated that women with PMOS exhibit elevated stimulated LH/FSH ratios compared to eugonadal controls. In response to GnRH stimulation, LH responses were exaggerated, leading to higher LH/FSH ratios at both 30- and 60-min post-stimulation. These disproportionate LH increments yield diagnostically informative stimulated LH/FSH ratios (LH/FSH ratio >1.72 at 60-min post-stimulation; sensitivity = 81.7%; specificity = 81.3% in diagnosing PMOS compared to controls), underscoring selective potentiation of LH output in PMOS.[53]

Similarly, sequential GnRH stimulation elicited two- to three-fold greater absolute LH increments in PMOS compared to controls alongside approximately a two-fold higher integrated LH output (mean serum LH over 12-h: 6.5 ± 0.9 IU/L in PMOS vs. 3.5 ± 0.3 IU/L in controls).[54] Notably, the percentage change in LH output did not differ between PMOS and controls, suggesting that the exaggerated rise in LH pulse amplitude in PMOS may reflect chronically raised basal LH rather than heightened pituitary sensitivity.[54]

In vivo chronic chemogenetic activation of GnRH neurons in female mice doubled LH pulse frequency, generating a sustained PMOS-like state: increased testosterone (1.96 ± 0.64 ng/mL in stimulated vs. 0.62 ± 0.25 ng/mL in control mice), increased pre-antral follicles (∼2-fold), elevated AMH (∼1.86-fold), and reduced pre-ovulatory follicles (∼4-fold) and corpora lutea (∼3-4-fold).[55] Accelerated LH pulse frequency persisted for 2 months following cessation of stimulation, indicating that transient hypothalamic dysregulation is sufficient to induce long-lasting reproductive dysfunction. The phenotype was rapidly abolished by GnRH antagonism, confirming that the pathology can be terminated using agents acting upstream of the pituitary gland.[55]

Moreover, experiments in ovariectomised global androgen-receptor (AR) knockout female mice, transplanted with wild-type ovaries show protection against the PMOS phenotype following dihydrotestosterone (DHT) treatment.[56] In contrast, wild-type females with ovary-specific AR deletion develop ovulatory dysfunction resembling PMOS, underscoring the importance of extraovarian AR signalling in driving the endocrine dysfunction. Neuronal AR signalling appears to be critical for the manifestation of PMOS features, as neuron-specific AR knockout models are protected from DHT-induced changes.[56] While GnRH neurons lack the receptors for steroid-mediated feedback, localisation of sex-steroid receptors within the upstream KNDy neurons and their inputs identified this area as a principal site for steroid-mediated feedback.[57,58] Collectively, these findings provide compelling evidence that the endocrine and ovarian abnormalities of PMOS can arise directly from hypothalamic dysregulation, even without primary ovarian defects.

Hyperandrogenism is thus strongly implicated in the pathophysiology of PMOS with chronically enhanced AR signalling and hyperandrogenism progressively establishing the conditions for neuroendocrine dysfunction.[59] In line with this, Silva et al. showed that early prenatal androgen exposure is sufficient to program the GnRH neuronal network, via enhanced GABAergic signalling on GnRH neurons, even before the manifestation of hyperandrogenism and reproductive deficits in PNA mice.[59] Nonetheless, long-term AR blockade in adulthood normalised GABAergic signalling onto GnRH neurons, restoring reproductive potential in PNA mice suggesting plasticity within these neuroendocrine circuits, which are likely maintained by excessive androgen signalling.[59] Similarly, Eagleson and colleagues demonstrated that a 5-week treatment with androgen receptor antagonism in women with PMOS restored the sensitivity of the GnRH pulse generator to feedback inhibition by E2 and progesterone, implicating chronically enhanced AR signalling in mediating the blunted sex-steroid mediated negative feedback observed in PMOS.[11] Nonetheless, the effects of acutely enhanced AR signalling are less clear with some studies failing to show an effect of acute AR block on baseline gonadotroph levels in post-menopausal women, possibly suggesting that enhanced AR signalling does not necessarily acutely impair the GnRH pulse generator.[60] However, it is important to note that these studies were performed in postmenopausal women with different underlying neuroendocrine signatures to women with PMOS. Interestingly, exogenous androgen administration in the concept of gender-affirming testosterone therapy (GAT) or anabolic substance use (synthetic testosterone derivatives) results in anovulation via a neuroendocrine mechanism which sits diametrically at the opposite end of the spectrum and is characterised by hypothalamic–pituitary–gonadal axis suppression and reduced LH secretion.[61] Possible mechanisms explaining the divergent neuroendocrine phenotypes of these hyperandrogenaemic conditions include different androgen concentrations (∼up to ×3 higher levels in individuals treated with GAT compared to PMOS individuals), different sources of androgen exposure (endogenous in PMOS vs. exogenous in GAT), different dosing regimens and timing of administration, although exactly how these factors interact to produce divergent outcomes is currently unclear.[61]

## 5 | KNDy HYPERACTIVITY IN PMOS

Direct human evidence of the overactive KNDy-GnRH pulse generator underscoring PMOS arises from pharmacological suppression of NKB signalling. In a phase II double-blind, placebo-controlled trial of AZD4901 (an antagonist of NK3R), women with PMOS receiving high-dose treatment (80 mg/day) exhibited a 3.55 per 8 h greater reduction in LH pulse frequency by day 7 compared with placebo, alongside a ∼79% reduction in basal LH secretion, ∼27% reduction in serum total testosterone, whilst FSH concentrations were unaffected.[62] LH mass per pulse was unchanged, indicating that the fall in total LH output resulted from reduced pulsatility and basal drive rather than reduced pituitary secretory capacity. The integrated LH exposure was reduced by ∼35% by day 28 in non-ovulating PMOS women. Together, these findings demonstrate that NKB/NK3R-dependent excitation of KNDy neurons is pathologically upregulated in PMOS and is a major determinant of LH hypersecretion.[62]

These findings were corroborated in a subsequent randomised, placebo-controlled trial of fezolinetant (another NK3R antagonist) over 12 weeks. Sustained reductions in LH (∼47%–70%), LH/FSH ratio (∼46%–54%), and serum testosterone (∼24%–37%) were observed in women with PMOS, confirming durable neuroendocrine suppression.[63]

Acute kisspeptin receptor (KISS1R/Kiss1r) agonism has also been investigated in PMOS. A proof-of-principle study by Romero-Ruiz et al. evaluated daily subcutaneous administration of kisspeptin-54 (KP-54) in three androgen-induced rat models of PMOS and in a pilot cohort of anovulatory women with PMOS.[64] Data, although heterogeneous, suggested partial capacity of kisspeptin in evoking gonadotrophin response and ovulation under certain PMOS conditions, with the greatest efficacy demonstrated in the PMOS model linked to early androgenisation, without a marked rise in serum androgen levels.[64]

Beyond KNDy neurons, additional afferent inputs contribute to GnRH hyperactivity in PMOS, particularly GABAergic ARC signalling. In contrast to its usual inhibitory action, ARC GABAergic signalling is stimulatory on GnRH neuronal cell bodies and proximal dendrites (Figure 1).[40,65] Optogenetic and immunolabelling studies consistently demonstrate GABAergic synaptic interactions with GnRH neuronal cell bodies and proximal dendrites across animal models, and in PNA mouse models these are increased while the proportion of $GABA^{ARC}$

neurons expressing PGRs is markedly reduced, implicating impaired steroid feedback at this upstream node.[48,66,67] Chronic $GABA^{ARC}$ neuronal activation over 3 weeks disrupts oestrous cyclicity, reduces proestrus frequency, and decreases corpus luteum formation, generating a PMOS-like ovarian phenotype, associated with a higher stimulated percentage rise in testosterone levels compared to controls, but without any significant changes in cumulative LH secretion.[68] These findings identify $GABA^{ARC}$ neurons as modulators of GnRH output capable of inducing sustained reproductive dysfunction when chronically activated.

AMH has also emerged as a central modulator of GnRH hyperactivity in PMOS. In PNA mouse models, AMH correlates strongly with LH concentrations ($R^2 = 0.71$), and type II AMH receptors (AMHR2) are expressed on a substantial proportion of GnRH neurons of the POA throughout development and adulthood (>50% in adult mice).[69] Intracerebroventricular administration of AMH in dioestrus female mice more than doubles LH pulse frequency and results in raised LH levels in a dose-dependent manner. This effect is abolished by pharmacological inhibition of AMH receptor signalling and by GnRH antagonism, suggesting a central action of AMH on GnRH neurons.[69,70]

## 6 | THE MODULATING EFFECT OF ADIPOSITY ON NEUROENDOCRINE DYSREGULATION IN PMOS

Obesity is present in 30%–75% of women with PMOS, although prevalence estimates vary, in part, due to referral bias.[71,72] Obesity confers an increased risk of PMOS largely through exacerbation of insulin resistance, chronic low-grade inflammation, and hyperandrogenism, which interact with and amplify intrinsic hypothalamic–ovarian dysfunction.[72]

Mendelian randomisation analyses have refined this association. In a large genetic study, one standard deviation increase in genetically-predicted BMI was associated with a modest 13% increased PMOS risk, which is substantially smaller than the ~87% increase suggested by observational estimates per standard deviation higher BMI.[73] This discrepancy between observed and genetically-predicted estimates underscores the acquired modifying effect of obesity-related metabolic dysregulation on the risk of developing PMOS.

Paradoxically, increased adiposity attenuates the classical neuroendocrine phenotype of PMOS, particularly abnormalities in LH pulsatility. This apparent dissociation has prompted the view that lean and obese PMOS represent distinct, though related, phenotypic subtypes. Hierarchical cluster analysis of 893 genotyped PMOS cases, incorporating anthropometric, reproductive and metabolic variables, identified two principal clusters; a 'reproductive' subtype (~23% of PMOS subjects) characterised by elevated LH and sex hormone binding globulin (SHBG) with relatively low BMI and insulin levels, and a 'metabolic' subtype (~37% of PMOS subjects) marked by higher BMI, glucose and insulin levels alongside lower LH and SHBG.[74] BMI emerged as the dominant discriminator between clusters, followed by insulin, SHBG, glucose, LH and FSH.[74]

Accordingly, lean PMOS typically exhibits a 'reproductive-dominant' phenotype with exaggerated neuroendocrine signatures: elevated basal LH, accelerated LH pulse frequency, and marked LH/FSH ratio. In contrast, obese PMOS is characterised by a 'metabolic-dominant' phenotype in which insulin resistance and adiposity predominate, while LH markers are attenuated, despite preserved acceleration of LH pulse frequency.[74]

### 6.1 | Adiposity attenuating the reproductive phenotype

Comparative studies consistently demonstrate an inverse relationship between BMI- and LH-related parameters within PMOS. In a study involving 33 women with PMOS and 32 controls, Arroyo et al. demonstrated that BMI correlates negatively with LH pulse amplitude ($r = -0.63$), mean 24-h LH concentrations ($r = -0.63$), and the LH/FSH ratio ($r = -0.44$) in PMOS, whereas no such associations are observed in controls.[75] At BMIs <30 kg/m$^2$, 95% of PMOS participants exhibited 24-h mean LH values exceeding the control range; however, at higher BMIs, 43% of PMOS participants could not be discriminated from controls based on LH alone.[75]

Pagan et al. showed that baseline LH concentrations in lean women with PMOS (mean BMI ~18 kg/m$^2$) were nearly 4-fold higher than in severely obese PMOS subjects (mean BMI ~47 kg/m$^2$).[76] Across the PMOS cohort, BMI correlated inversely with mean LH ($r = -0.606$), the LH/FSH ratio ($r = -0.627$), and LH pulse amplitude ($r = -0.626$), while LH pulse frequency remained elevated but unaffected by BMI.[76] Additionally, following exogenous GnRH administration, obese women with PMOS exhibited significantly attenuated peak LH responses ($r = -0.475$) and reduced integrated LH secretion ($r = -0.412$).[76]

In obese PMOS, accelerated GnRH pulsatility remains detectable at the hypothalamic level, yet its hormonal expression is attenuated, manifesting as reduced LH pulse amplitude, lower basal LH concentrations, and blunted responses to GnRH stimulation.

A central mediator of this attenuation is hyperinsulinaemia and insulin resistance. Multivariable modelling demonstrates that the interaction between insulin and BMI is the strongest predictor of mean LH in PMOS (LH = insulin + BMI + insulin × BMI; $R^2 = 0.614$), exceeding simple additive models (LH = insulin + BMI; $R^2 = 0.455$) and demonstrating a synergistic inhibitory effect of adiposity and hyperinsulinaemia on LH secretion.[77]

Insulin resistance is also associated with higher leptin levels and hyperinsulinaemia has been linked to raised leptin transcription in adipocytes, possibly reflecting the role of insulin in stimulating leptin secretion.[78] Under physiological conditions, leptin provides a permissive signal of energy sufficiency to reproductive circuits.[79] Serum leptin levels are higher in women with obesity (BMI ≥ 25 kg/m$^2$) and PMOS compared to BMI-matched controls, whereas in those with BMI <25 kg/m$^2$, there was no significant difference between PMOS and controls.[78] This possibly underscores the impact of hyperinsulinaemia in 'metabolic-predominant' PMOS phenotypes.

Double-label in situ hybridisation studies identified a 42% ± 4% co-expression of leptin receptor (*LepR*) in mice *Kiss1*$^{ARC}$ mRNA expressing cells.[80] Chronic hyperleptinaemia in obesity, however, produces central leptin resistance, characterised by reduced hypothalamic LepR-B (leptin receptor B) expression and impaired signalling.[81] Leptin normally suppresses upstream neuropeptide Y/Agouti-related peptide (NPY/AgRP)-mediated inhibition of GnRH and kisspeptin neurons.[82] Thus, leptin resistance might act partly by modulating these upstream pathways. However, while both leptin and insulin resistance have been implicated in the pathogenesis of PMOS, the mechanistic framework of how they contribute centrally to PMOS remains to be further characterised.

Accelerated LH clearance further contributes to reduced circulating LH in obesity. LH circulates as multiple isoforms, and higher BMI is associated with increased production of sulfonated isoforms, with shorter half-lives and faster metabolic clearance.[83] Pharmacokinetic analyses demonstrate a negative correlation between LH half-life and BMI ($r = -0.46$) and a positive correlation between BMI and endogenous LH clearance ($r = 0.53$).[14]

Obesity-associated inflammation exerts inhibitory effects on the reproductive axis. Women with obesity exhibit elevated circulating proinflammatory cytokines, including IL-1β and TNF-α.[13] These suppress GnRH and LH release in ovariectomised rats.[84] In diet-induced metabolic syndrome models, LH correlates negatively with IL-6 ($r = -0.466$).[85] Acute inflammatory challenges similarly suppress LH secretion (>50%) and kisspeptin expression (∼30%), effects which are reversed by exogenous kisspeptin, confirming inflammation as a potent central inhibitor of GnRH-LH signalling.[86]

Importantly, LH pulse frequency remains elevated in obese PMOS, in line with persisting hypothalamic dysregulation. The attenuation of circulating LH therefore reflects superimposed metabolic constraint rather than resolution of GnRH hyperactivity.

## 7 | CLINICAL IMPLICATIONS AND DIAGNOSTIC CHALLENGE

The attenuating effect of adiposity on LH secretion carries important diagnostic consequences. In a study by Morales et al., mean LH pulse amplitude in obese women with PMOS was approximately half that observed in lean PMOS (6.4 ± 0.7 vs. 13.3 ± 2.8 IU/L) and closely overlapped with both obese and lean controls (5.3 ± 0.49 and 5.0 ± 0.5 IU/L, respectively).[45] Given the high prevalence of obesity in women with PMOS, this attenuation can obscure the classical neuroendocrine hallmarks of the syndrome in routine evaluation and create a clinically important source of misclassification. Women with obesity presenting with anovulation may incorrectly be labelled as having PMOS when, in fact, they exhibit female obesity-related secondary hypogonadism (FOSH).[12] FOSH is characterised by reduced hypothalamic drive, diminished LH secretion and enhanced oestradiol-mediated negative feedback, features fundamentally distinct from the hypothalamic hyperactivity underlying PMOS.[12]

A critical discriminator between these two entities remains the LH pulse frequency. Obese women with PMOS retain elevated LH pulse frequency, which is largely BMI-independent.[76] In contrast, eumenorrheic women with obesity exhibit LH pulse frequencies indistinguishable from normal-weight controls, reflecting preserved but downregulated hypothalamic output.[87]

Recognition of obesity's modifying effect on the PMOS phenotype has begun to influence guideline development. While the Rotterdam criteria do not incorporate LH concentrations or LH/FSH ratios, updated Japanese PMOS guidelines, where prevalence of obesity is less prominent, do include elevated LH as a diagnostic component.[88]

Additionally, Gao et al., have used cluster analysis based on nine variables (LH, FSH, AMH, SHBG, testosterone, dehydroepiandrosterone sulphate (DHEAS), BMI, fasting glucose, and fasting insulin) to subclassify PMOS into four distinct subtypes; hyperandrogenic (HA-PMOS), obese PMOS (OB-PMOS), high SHBG PMOS (SHBG-PMOS) and high-LH-AMH subtype (LH-PMOS), with each subtype approximately representing a quarter of the PMOS population.[89] Each subtype is associated with distinct biochemical and clinical profiles that predict clinical outcomes after fertility treatment. This helps identify category-specific risk factors and associated complications aiming to tailor treatment approaches and predict responses and disease progression.[89] Nonetheless, these subtypes may be dynamic, with intra-individual phenotypes changing as women progress through their reproductive lifespan. This may support a shift away from clustering and towards predictive modelling as a tool for longitudinal prediction of clinical outcomes.

## 8 | THERAPEUTIC INSIGHTS: MODIFYING NEUROENDOCRINE DYSFUNCTION THROUGH WEIGHT-TARGETED INTERVENTIONS

Within the 'metabolic-dominant' PMOS subtype, interventions targeting obesity and insulin resistance can, at least partly, induce remission of diagnostic features, underscoring the partial reversibility of the syndrome with sustained improvement in metabolic factors.

In a study of 144 obese women with PMOS (mean BMI = 35 kg/m$^2$), diet-induced weight loss of more than 5% ameliorated hyperandrogenism (25% reduction in free testosterone) and metabolic disturbances (∼72% reduction in fasting insulin) and translated into improved ovulatory capacity with about a third of the women with menstrual irregularities reverting to regular cycling and about one tenth of amenorrhoeic women resuming menstrual cycles, underscoring at least partial reversibility of the PMOS phenotype following improved metabolic profiles.[90]

Short-term treatment with metformin, an insulin sensitiser, for 4–6 weeks in non-obese women with PMOS produces marked endocrine effects, including reduced free testosterone (∼70%) and fasting serum insulin (∼57%), and attenuated LH response to GnRH stimulation.[91] In a randomised trial, metformin increased menstrual frequency from 0.22 ± 0.04 to 0.59 ± 0.07 cycles/month per patient, while

~55% of women demonstrated significant improvements in their menstrual cycles, with 79% of cycles being ovulatory.[92] These findings support the view that hyperinsulinaemia exaggerates LH release, and that its correction can restore, at least partly, normal gonadotroph function.

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are now incorporated as a therapeutic option in contemporary PMOS guidelines.[93] GLP-1 administration in female rats enhances the pre-ovulatory LH surge, increases luteal progesterone production (1.7-fold), and improves ovulatory parameters (increased number of Graafian follicles by ~2.3-fold; corpora lutea by ~1.35-fold).[94] These effects are accompanied by upregulated hypothalamic *Kiss1r* expression during proestrus, suggesting that GLP-1 may act, at least partly, through activation of kisspeptin-dependent GnRH signalling pathways.[94] Recent data support a role for GLP-1RAs in women with PMOS and BMI ≥25 kg/m$^2$. A meta-analysis of seven randomised controlled trials (RCT) comparing liraglutide with metformin, placebo, or alternative therapies demonstrated a substantial increase in menstrual frequency (Hedges' $g = 1.76$), alongside improvements in metabolic parameters, including reductions in BMI and insulin resistance surrogates (Homeostatic Model Assessment of Insulin Resistance; HOMA-IR) (Hedges' $g = -0.52$ for both).[95] Although reproductive outcomes were reported in only two studies, both demonstrated favourable results with liraglutide compared to metformin. In one of the studies, pregnancy rates at 1 year were higher (69.2% vs. 35.7%), as were pregnancy rates per embryo transfer (85.7% vs. 28.6%), accompanied by increased dominant follicle formation, albeit the sample size was relatively small.[95] However, given the limited data available reporting hard reproductive endpoints, conclusions regarding long-term reproductive benefit remain provisional and care needs to be taken not to use these medications in women who may become pregnant.[95] Importantly, cessation of GLP-1RAs is associated with rapid weight regain, with up to 60% of the weight lost estimated to be regained within 1 year of cessation, and subsequent weight regain modelled to plateau at 75.3% of the weight lost while on treatment.[96] Consideration should thus be made for weight management strategies in women planning to conceive following cessation, since GLP-1RAs are not licensed in this cohort.

Bariatric surgery represents the most potent metabolic intervention. In PMOS rat models, sleeve gastrectomy restores oestrous cyclicity and normal follicular architecture within just 3 weeks of intervention. These changes are associated with normalisation of *Kiss1*$^{ARC}$ mRNA expression by 3 weeks, implicating hypothalamic reprogramming in ameliorating the PMOS phenotype.[97] Translational potential has also been demonstrated: in a prospective study of 18 obese women with PMOS undergoing sleeve gastrectomy, the LH/FSH ratio decreased by ~40%, driven by a fall in LH by ~38%, indicating partial restoration of physiological gonadotroph balance.[98] In the Bambini trial, a multicentre open-label RCT of women with PMOS and BMI ≥35 kg/m$^2$, vertical sleeve gastrectomy produced a 2.5-fold increase in spontaneous ovulation rates over 52 weeks compared with medical therapy, alongside greater reduction in AMH, greater increase in SHBG, and superior improvements in body weight and HOMA-IR.[99] Collectively, these interventions demonstrate that the neuroendocrine phenotype observed in obese PMOS is predominantly metabolically driven and dynamically modifiable.

## 9 | FUTURE DIRECTIONS

The heterogeneity of PMOS underscores the need to move beyond syndromic diagnostic criteria towards precision phenotyping. Current classifications inadequately capture the variable contribution of neuroendocrine, metabolic, and ovarian dysfunction. Future research should prioritise phenotyping approaches, combining neuroendocrine dynamics (GnRH/LH pulsatility), metabolic profiling, ovarian biomarkers, and genetic susceptibility to define biologically meaningful prediction of risk capable of directing optimal management. Such stratification may facilitate personalised therapeutic strategies, particularly across the body mass spectrum.[89]

A second priority is the therapeutic modulation of the GnRH/KNDy pulse generator as a targeted neuroendocrine intervention. Recent clinical trials demonstrating suppression of LH secretion with NK3R antagonists highlight the translational potential of targeting KNDy neuronal signalling.[63] The recent licensing of NKB antagonists for the treatment of menopausal vasomotor symptoms further underscores the broader therapeutic potential of modulating KNDy neuronal pathways.[100]

## 10 | CONCLUSION

PMOS is a complex metabolic-reproductive disorder in which accelerated GnRH pulsatility represents a central neuroendocrine abnormality. Increased GnRH pulse frequency, potentiated by impaired steroid-mediated negative feedback at the level of the hypothalamic pulse generator, preferentially stimulates LH secretion from the pituitary and promotes ovarian hyperandrogenism and anovulation.

Adiposity modifies this neuroendocrine landscape. Obesity imposes metabolic limitations that attenuate LH amplitude and basal concentrations. This contributes to phenotypic heterogeneity and limits the utility of static gonadotrophin measurements, particularly in higher-BMI populations. Nonetheless, LH pulse frequency remains persistently elevated and BMI-independent, and while in theory it could be exploited for diagnostic purposes following determination of clinically useful cut-offs, it remains a costly and labour-intensive investigation; hence, it is currently limited to the research capacity.

Therapeutic observations reinforce the interplay between metabolism and neuroendocrine function. Weight-targeted interventions consistently improve ovulatory and metabolic outcomes in women with obesity and PMOS, suggesting that reproductive dysfunction may be driven partly by reversible metabolic dysregulation.

Together, these findings highlight the need to integrate neuroendocrine dynamics in PMOS with metabolic context. Precise phenotyping alongside development of targeted therapeutic strategies will be

transformative in addressing the heterogeneity of PMOS and improving reproductive and metabolic outcomes.

## AUTHOR CONTRIBUTIONS

**Anna Kyriakidou:** Writing – original draft. **Kanyada Koysombat:** Writing – original draft. **Alexander N. Comninos:** Writing – review and editing. **Waljit S. Dhillo:** Writing – review and editing. **Ali Abbara:** Writing – review and editing; supervision.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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