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Is the brain driving polyendocrine metabolic ovarian syndrome?

SUMMARY
Polyendocrine metabolic ovarian syndrome (PMOS) is traditionally viewed through the lens of the ovary, but its origins may lie much earlier — in the brain. Kisspeptin, neurokinin B, and dynorphin (KNDy) neurones play a central role in regulating the rhythms of female reproduction. Changes in their activity, potentially influenced by chronic stress, may disrupt the brain–ovary conversation, contributing to anovulation and ovarian dysfunction.

For decades, the ovary has stood at the centre of female reproductive medicine. Yet, the critical instructions that tell the ovary when to mature a follicle and release an egg originate much farther away—deep within the brain.

Within the hypothalamus is a small cluster of cells known as KNDy neurones. Acting as the ultimate conductors of the body's reproductive symphony, these neurones release carefully timed chemical signals to regulate the hypothalamic-pituitary-gonadal (HPG) axis. By controlling pulses of gonadotropin-releasing hormone (GnRH), KNDy neurones precisely set the pace of the body's reproductive clock. But when this finely tuned neural rhythm is disrupted, the effects can ripple through the HPG axis, ultimately altering ovarian function.

When the rhythm becomes chaotic

Reproduction depends entirely on precise timing. When KNDy neurones become hyperactive, they no longer act as a finely tuned conductor and instead behave like a loudspeaker blaring at full volume.

This neural hyperactivity overwhelms the pituitary gland, disrupting the carefully coordinated secretion pattern of downstream reproductive hormones. Caught in a state of constant hormonal confusion, ovarian follicles are denied the steady, rhythmic cues required to support normal growth and maturation. Rather than progressing naturally towards ovulation, follicular development stalls midway through the cycle. This central breakdown is a key feature of PMOS, leaving otherwise healthy follicles unable to complete their journey and contributing to anovulation and infertility (Figure 1, overleaf).

When stress strikes

The brain does not misfire in a vacuum; it constantly responds to environmental threats. Chronic stress is one of the most potent triggers capable of knocking the KNDy neural network out of balance.

Chronic stress exposure has been shown to induce a cascade of reproductive dysfunction in laboratory rats, ultimately leading to disruption of the regular ovulatory cycle. Rather than protecting the body, the brain's stress response inadvertently sabotages its own fertility machinery. These findings suggest that stress, disrupted neural signalling, and ovarian dysfunction are not separate events, but rather different chapters of the same story.

The Genetic Cross-Talk Behind Cysts

There is another key element to this story: metabolism. Reproduction and metabolic health are deeply intertwined, and the brain acts as the central hub bridging both systems.

To understand how anovulatory follicles develop into fluid-filled cysts, postmortem genetic analysis of brain and ovarian tissues offers important clues. Researchers have uncovered a striking correlation between the expression of KISS1—the key gene driving KNDy neuron signalling—and

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pathways involved in insulin signalling. This genetic cross-talk between reproductive neurones and metabolic pathways suggests that hyperactive KISS1 signalling, combined with altered insulin responses, may interfere with ovulation. Unable to rupture and release the egg, the follicles remain trapped within the ovary, gradually swelling into cysts and contributing to one of the defining physical hallmarks of PMOS.

Could the brain be the starting point?

This does not mean PMOS has a single cause—far from it. PMOS remains a complex, multi-faceted condition involving interactions between the reproductive, endocrine, and metabolic systems.

However, looking beyond the ovary at the brain–pituitary–ovary axis opens a powerful new perspective. If stress-induced changes in KNDy activity disrupt reproductive rhythms while also influencing metabolic pathways, altered brain signalling may be a primary driver in the development of ovarian cysts. The ovary remains central to the story, but it may not be where the story begins.

A new way of looking at PMOS

Understanding the brain's role in reproductive dysfunction could eventually change how we think about PMOS.

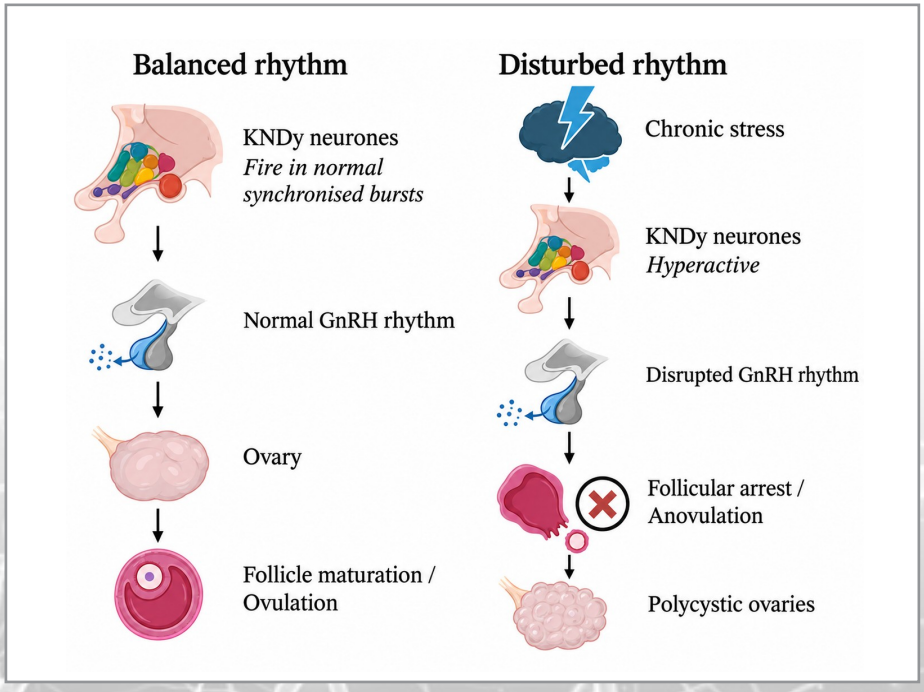
Instead of seeing the condition solely as a disorder of the ovary, researchers are beginning to consider it as a disruption in communication between interconnected systems— the brain, reproductive organs and metabolic pathways.

KNDy neurones could be an important piece of this puzzle. By understanding how their activity is regulated, how stress alters reproductive signalling, and how reproductive and metabolic pathways interact, we may gain a clearer understanding of how the body's finely tuned fertility rhythm becomes disrupted.

"The ovary remains central to the story, but it may not be where the story begins."

Perhaps the next chapter in the PMOS story will not begin in the ovary at all — but further upstream, in the brain.

Figure 1. The brain–ovary conversation in PMOS.



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