

Menstrual Cycle Misfire: When Biochemistry Meets Burnout

by

Megna Tiwari and Erin L. Dolan

Department of Biochemistry and Molecular Biology

University of Georgia, Athens, GA

Part I – The Disrupted Rhythm

Maya, a medical student and long-distance runner, walked into her medical school's endocrinology clinic for what she thought would be a routine check. She hadn't had her period in over three months, but she shrugged it off and attributed it to her marathon training. Her clinician, Dr. Morales, noted that Maya trained six days a week, running a total of 60–70 miles, and maintained a strict “clean eating” regimen heavy in protein, but light on overall calories. Maya was balancing medical coursework, tutoring shifts, and late-night study sessions. Sleep was short. Stress was high. When asked about other symptoms, Maya mentioned fatigue, irritability, and occasional lightheadedness. She insisted she was “fine”; if anything, she felt stronger than ever. But Dr. Morales was concerned and ordered a standard hormonal panel. Missing periods was common in endurance athletes, yet Maya's case felt less straightforward. Her physical fitness appeared excellent, but her physiological signals might be telling a different story. Dr. Morales understood how subtle biochemical shifts could disrupt communication between the brain and the reproductive system. Sometimes a simple “missed period” revealed a deeper layer of biological regulation.

A few days later, Maya returned to the clinic for her test results. The nurse handed her a printout while Dr. Morales finished another appointment, and gave Maya a few minutes to look over the numbers herself.

Table 1. Maya's hormone panel.

Hormone	Maya's Value	Reference Range	Interpretation
Follicle-stimulating Hormone (FSH)	6.1 IU/L	3–10 IU/L	Normal
Luteinizing Hormone (LH)	19.0 IU/L	2–15 IU/L	Slightly elevated
Estradiol	20 pg/mL	30–400 pg/mL	Low
Progesterone	3 ng/mL	5–20 ng/mL (expected luteal phase)	Slightly Low

At first glance, most hormone concentrations fell within or near their reference ranges. However, laboratory reference intervals alone do not necessarily indicate normal physiological function. When Dr. Morales walked in, she glanced at the report, frowned slightly, and asked Maya to schedule a follow-up appointment with an endocrinology research lab for a deeper evaluation. The clinic routinely partnered with the research lab at the university's teaching medical school when hormone levels and physiological symptoms did not line up, and Maya's case fit that pattern. Therefore, Maya was offered the opportunity to participate in additional laboratory analyses that were not part of routine clinical testing. As Maya left the clinic, she couldn't help but stare at the sheet in her hand: the data seemed to say she was fine, but something in her body clearly wasn't.

Questions

- Before looking more closely at Maya's hormone panel, brainstorm one to three physiological mechanisms that could explain a missed period in a competitive endurance athlete. What additional information would help distinguish among your hypotheses?
- Examine Maya's hormone panel (Table 1). Which results stand out and what patterns do you notice?
- Using the hypothalamic-pituitary-ovarian (HPO) axis schematic (Figure 1), how would you describe the communication and feedback among the hypothalamus, pituitary, and ovaries based on these data? Where might communication be disrupted?

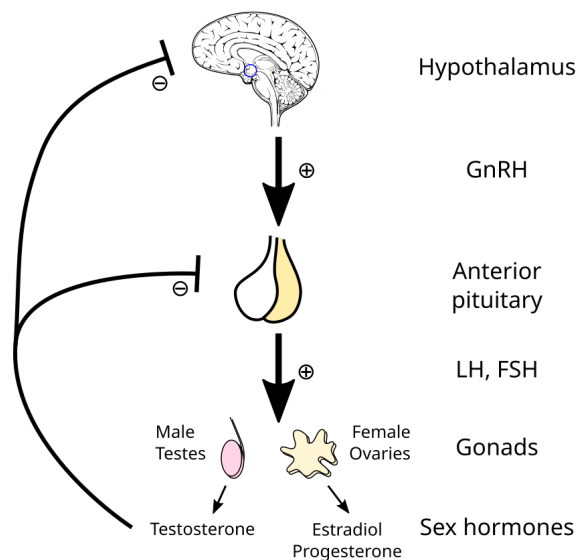


Figure 1. The hypothalamic-pituitary-ovarian (HPO) axis.
Credit: Wikimedia Commons | Artoria2e5, CC BY 3.0.

- If Maya's hormone concentrations appear mostly normal, what factors could interfere with how these hormones actually work in the body? Brainstorm some ideas (hypotheses).

Part II – The Bioactivity Puzzle

A week later, Maya arrived at the endocrinology lab for a deeper evaluation. A graduate researcher, Noah, greeted her and explained that the first step was to measure how Maya's LH behaved in a functional assay. Unlike the clinic's earlier test, which measured LH concentration, this experiment examined how strongly Maya's LH activated LH receptors in cultured ovarian cells. Maya's sample was processed alongside recombinant LH, which is a commercial form of healthy LH. After incubation, the receptor activation data were generated and plotted. Noah looked at the curves side-by-side, jotting down notes (Figure 2). He did not share conclusions or interpretations; he simply told Maya that the results were "interesting" and that they would run additional analyses to better understand what they were seeing.

Use Figure 2 to answer the questions below.

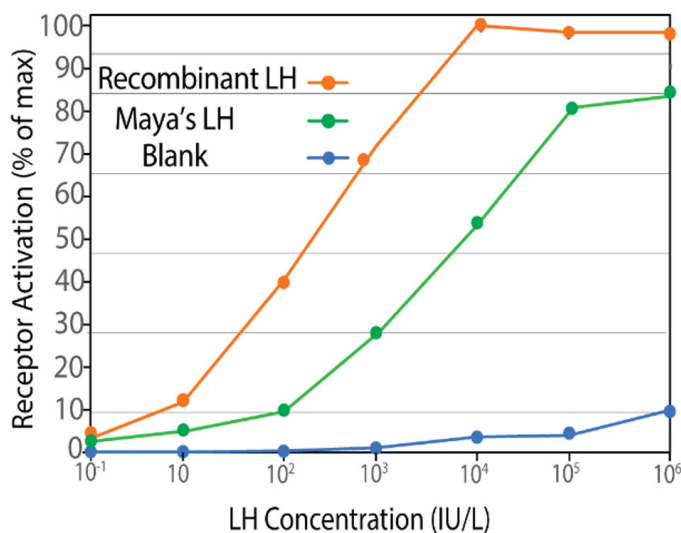


Figure 2. LH receptor activation (% of maximum signaling) was measured across a range of LH concentrations (10^{-1} – 10^6 IU/L) for three samples: Maya's LH (green), recombinant LH (orange), and a blank control (blue). Each point represents the measured receptor response at a given LH concentration in the bioassay. *Credit:* Adapted from Klett and Combarnous (2021).

Questions

- Which LH sample is the positive control? Why do you think so or how do you know?
- Which LH sample is the negative control? Why do you think so or how do you know?
- Compare Maya's LH and the healthy LH at the same concentrations: what similarities or differences do you notice in their dose–response curves? List at least two conclusions.
- Based solely on the trends in the graph, what initial ideas can you propose about how these LH samples might differ?

Part III – The Architecture of LH

Before conducting the final analyses, Noah gave Maya a quick primer on the hormone they were about to examine. He explained that LH was not just a simple protein, it was a glycoprotein, meaning that the protein was decorated with specific glycans (sugars) at defined sites. These glycans form branching sugar structures that contribute to LH's overall architecture and can influence how the hormone circulates in the body, as well as how it binds to and activates its receptor. Noah also highlighted one key structural feature that would become important later: the β -subunit of the protein is responsible for receptor recognition and binding, whereas the α -subunit is shared among several pituitary glycoprotein hormones and helps maintain the hormone's overall structure.

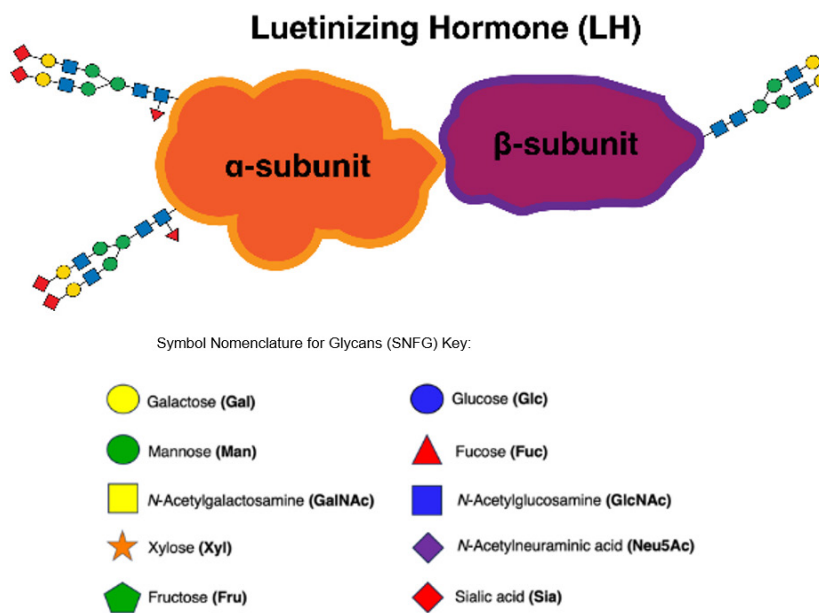


Figure 3. Simplified schematic of luteinizing hormone (LH). The α - and β -subunits are shown with their N-linked glycans. The α -subunit (orange) contains two N-linked glycans, while the β -subunit (purple) contains one N-linked glycan. Glycans are illustrated using standard symbol nomenclature for glycans (SNFG) monosaccharide symbols.

Noah explained that scientists have long known that changes in glycosylation can influence how glycoprotein hormones behave. For example, altering the composition or arrangement of attached sugars can affect how long a hormone remains in circulation and, in some cases, its biological activity. He introduced the concept of hormone half-life, the amount of time a hormone remains in the bloodstream before being cleared by the body. He also explained that both the protein itself and its attached glycans can contribute to this process. Noah emphasized that, although the effects of glycosylation on hormone behavior are well established, how these structural changes contribute to specific physiological conditions is less clear and remains an active area of research. Their goal was not to confirm a known diagnosis, but to determine whether Maya's LH showed structural features that might help explain the disconnect between her laboratory results and clinical symptoms.

Finally, Noah explained that the lab's next experiment would involve a separation and detection method called mass spectrometry, which could reveal subtle differences in a protein's structure by measuring characteristics such as mass and charge. The goal was to compare Maya's LH with a reference sample at a deeper structural level.

Questions

9. Compare the glycans attached to the two LH glycoforms. How many of each type of monosaccharide are present in each structure? Are there any structural differences between the alpha and beta subunit glycan chains?
10. How might the addition or removal of glycans influence measurable properties such as mass of a protein even though the protein sequence stays the same?
11. LH's half-life refers to how long it stays in the bloodstream before being cleared. Propose and justify two hypotheses why glycosylation might affect LH's half-life (a general explanation is enough).

Part IV – The Hidden Difference

When the results were ready, Maya, who happened to be studying the HPO axis in medical school, asked to review and better understand her data. Noah brought her to the mass spectrometry workstation to examine the results together (Figure 4). He explained that each peak represented a group of LH molecules sharing similar structural characteristics. The lab did not need the exact structures, just a sense of how the overall pattern compared with what is typically seen. Even without interpretation, the comparison was striking. Noah circled several areas on the printout, noting that mass spectrometry was extremely sensitive and even small structural differences would show up in patterns like this. He told Maya the results would be reviewed carefully alongside her earlier tests. Maya left the clinic with one clear impression: her LH didn't follow the usual pattern. However, she still had no idea what that meant for her menstrual cycle or her overall health.

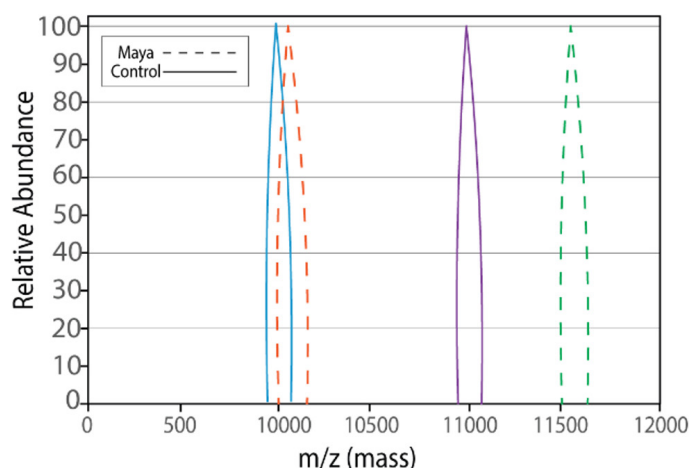


Figure 4. Mass spectra of LH α - and β -subunits for Maya's LH vs control LH. This representative figure shows the major mass peaks for the α - and β -subunits of luteinizing hormone (LH) after subunit separation and peptide fragmentation. Peaks for the α -subunit appear at approximately m/z 10,000 (control) and m/z 10,050 (Maya's sample). For the β -subunit, the control sample has a peak near m/z 11,000 whereas Maya's β -subunit shows a peak at 11,600.

Important notes: Small shifts of ± 25 –50 m/z are expected due to instrument noise and minor glycan variation. However, in this simplified dataset, adding monosaccharides, such as a sialic acid, a common terminal sugar on N-linked glycan chains, produces predictable increases in mass (~ 300 m/z per added sugar). Differences in peak positions therefore reflect variation in glycan size or composition across samples.

Questions

12. Compare the α -subunit peaks for the control and Maya. Do the differences in their m/z values suggest a meaningful structural change? Why or why not?
13. Examine the β peaks. How do the observed differences exceed normal variation, and what does this imply about structure?
14. Using the information from your responses to Questions 12 and 13 and the CER framework listed below, explain which LH subunit (α or β) appears to differ structurally between Maya and the control. Support your explanation with evidence from the mass spectra.
 C – Claim: State which subunit you think is different.
 E – Evidence: Identify the specific peak(s) in the figure that support your claim.
 R – Reasoning: Explain why the difference in peak position indicates a structural change in that subunit.
15. Considering that LH activity may be influenced by its glycan composition, propose one potential biological consequence of the mass shift you observe on the spectra.

Part V – Resolution and Recovery

Maya now understood that the differences seen in her mass spectrometry results were not due to changes in the LH protein sequence, but rather to differences in the glycans attached to it. Dr. Morales and Maya talked through the results together, recognizing that something about LH's structure was not matching its function. Instead of jumping to conclusions, Dr. Morales encouraged Maya to think through the results with her and promised that they would work out a full diagnosis at their next visit. Dr. Morales reminded Maya that ovulation depends on LH successfully binding and activating its receptor on ovarian cells. If LH signaling is weakened, the downstream events required for ovulation and normal production of estradiol and progesterone may also be disrupted. However, whether and how Maya's lifestyle and physiological stressors were related to the biochemical differences observed in her LH remained an open question. Maya's challenge was to determine whether the biochemical evidence collected thus far could explain this disconnect. Maya was now faced with three key clues: the structure of her LH, the function (i.e., activity) of her LH, and the overall glycosylation pattern of her LH hormone.

Rather than pointing to a single established mechanism, these findings challenged Maya to integrate biochemical and physiological evidence to develop a scientifically plausible explanation for how changes in LH glycosylation could contribute to her symptoms.



Consult with your instructor concerning which of the following assignments you should complete.

Reflection

In no more than 250 words, using evidence presented in this case study, explain how altered LH glycosylation could disrupt communication within the HPO axis and ultimately contribute to Maya's missed menstrual cycles. In your explanation, consider how lifestyle-related physiological stressors, including intense exercise, low energy availability, stress, and inadequate sleep, might be associated with the observed changes. Then predict how reducing these stressors could affect LH bioactivity and reproductive function. You do not need to be "correct"; focus instead on building a thoughtful, evidence-informed explanation that puts the puzzle pieces together.

For your reflection, synthesize what you have learned across these clues. How might a hormone like LH appear "normal" in concentration but still produce a weak or altered physiological signal? What role could its structure, particularly its glycan composition, play in shaping its biological activity? Consider how the mass shifts you observed, Maya's hormone panel, and her training or lifestyle factors might connect.

Group Activity

Working in groups of three to four, you will assign yourselves one of the roles below. From your assigned perspective, discuss how Maya's LH can appear "normal" in amount but produce a different physiological response.

- *Hormone Detective:* Use Maya's symptoms and hormone panel to determine why reproductive signaling appears abnormal despite normal LH levels.
- *Protein Biologist:* Use LH structure and mass spectrometry data to evaluate whether the change lies in the protein backbone or its attached glycans.
- *Receptor Analyst:* Use receptor activation data to explain how Maya's LH differs functionally from control LH.
- *Glycan Specialist:* Explain how altered glycosylation connects LH structure, function, and physiological outcome.

Hint: Use all your evidence from clues in the case study to build a single "big picture" explanation that connects molecular structure, LH function, and reproductive physiology. Consider whether aspects of Maya's lifestyle history could help explain the biochemical findings. Do you think Maya's condition is reversible? If so, how?