12b. Neuroendocrinology of reproduction

Unit 12B: Neuroendocrinology of Reproduction (HPO Axis)

Learning Goals

By the end of this lesson, you should be able to:

- diagram the **hypothalamic–pituitary–ovarian (HPO) axis** and the route of portal circulation;
- explain **GnRH pulsatility**, the **LH/FSH** response, and **ovarian feedback** by oestrogen, progesterone, inhibin/activin/follistatin;
- map neuroendocrine events across the **menstrual cycle**, **puberty**, **lactation**, **pregnancy**, and **menopause**;
- recognise how **prolactin, thyroid, adrenal, metabolic and stress** signals modulate the axis;
- interpret common clinical patterns (FHA, PCOS, POI, hyperprolactinaemia) and justify investigations and first-line management.

---

1) Organisation of the HPO Axis

Anatomical tiers

1. **Hypothalamus**—mainly **arcuate nucleus (ARC)** and **preoptic area** neurons release **GnRH** (decapeptide) into the **median eminence**. Blood enters the **hypophyseal portal system**, carrying GnRH in pulses to the anterior pituitary.
2. **Anterior pituitary (adenohypophysis)**—**gonadotrophs** synthesize and secrete **LH** and **FSH** in response to each GnRH pulse.
3. **Ovary**—**theca** and **granulosa** cells produce **oestrogens (E2)**, **progesterone (P4)**, **inhibin A/B**, **activin**, **follistatin**. These feed back to both pituitary and hypothalamus.

Why pulsatile?
GnRH receptors desensitise with continuous exposure. **Pulsatile GnRH (frequency + amplitude)** is required to keep the pituitary responsive. Therapeutically, **continuous GnRH agonists** (after initial flare) suppress the axis and are used for endometriosis, fibroids, and IVF down-regulation.

The pulse generator—KNDy concept
A small network of **Kisspeptin–Neurokinin B–Dynorphin (KNDy)** neurons in the ARC acts as the intrinsic pacemaker:

- **Kisspeptin** strongly stimulates GnRH neurons (via **KISS1R**).
- **Neurokinin B** (NKB) provides excitatory synchrony among KNDy neurons.
- **Dynorphin** provides inhibitory tone, shaping **inter-pulse interval**.
  Oestrogen modulates KNDy activity—supporting **negative feedback** during most of the cycle and switching to **positive feedback** in the late follicular phase.

Additional neuromodulators

- **GnIH (RFRP-3)**: inhibitory input to GnRH neurons (anti-gonadotropic).
- **Leptin, insulin**: metabolic signals that permit normal pulsatility.
- **Cortisol and CRH**: stress-related suppression.
- **Dopamine**: primary inhibitor of prolactin; indirectly supports GnRH by keeping prolactin in check.

---

2) Ovarian Hormones and Feedback Logic

Oestrogen (E2)

- **Source**: granulosa cells (aromatase converts thecal androgens to oestrogen).
- **Low–moderate E2**: **negative feedback** on GnRH and LH/FSH.
- **Sustained high E2** for ~36 hours (late follicular phase): flips the system to **positive feedback**, causing the **LH surge** (and smaller FSH surge).

Progesterone (P4)

- **Source**: corpus luteum (post-ovulation); placenta later in pregnancy.
- **Action**: slows GnRH pulse frequency, stabilises endometrium, raises basal body temperature by ~0.3–0.5°C.

Inhibin/Activin/Follistatin

- **Inhibin B** (granulosa of small antral follicles) selectively **suppresses FSH** in early–mid follicular phase.
- **Inhibin A** (corpus luteum) suppresses FSH in luteal phase.
- **Activin** enhances FSH synthesis; **follistatin** binds activin, thus **reducing FSH**.

Summary table

Signal	Main source	Phase prominence	Net feedback
Oestrogen (low–moderate)	Follicle	Early–mid follicular	Negative on GnRH/LH/FSH
Oestrogen (sustained high)	Dominant follicle	Late follicular	**Positive** → LH surge
Progesterone	Corpus luteum	Luteal	Slows pulses; negative overall
Inhibin B	Growing follicles	Early–mid follicular	Lowers FSH
Inhibin A	Corpus luteum	Luteal	Lowers FSH

---

3) Pulses, Frequencies and Cycle Dynamics

Early–mid follicular phase

- **GnRH pulses**: relatively **fast** (≈60–90 min).
- **Pituitary bias**: higher **LH** synthesis relative to FSH; FSH still sufficient to recruit a cohort of follicles.
- **Selection**: one follicle gains dominance via better FSH receptor expression, local IGFs, and decreased AMH locally.

Late follicular phase → Ovulation

- Dominant follicle raises **E2** to sustained high levels; this **sensitises** GnRH neurons and pituitary to generate a **mid-cycle LH surge**.
- **LH surge** triggers:
  - oocyte meiosis I completion and ovulation,
  - luteinisation of granulosa/theca,
  - cumulus expansion and follicular rupture.

Luteal phase

- **P4** slows GnRH pulses (e.g., 3–4 hourly) and reduces LH amplitude; FSH remains low due to **inhibins**.
- In absence of pregnancy, corpus luteum regresses → fall in P4/E2 → endometrial shedding; loss of negative feedback allows **FSH rise** to start the next cycle.

Arcuate vs preoptic control

- **Arcuate KNDy** drives **pulsatile** secretion throughout the cycle.

- **Preoptic area** contributes to the **surge** generation under sustained E2 conditions.

---

4) Neuroendocrinology Across Life Stages

Foetal and neonatal periods

- Transient activation ("**mini-puberty**") after birth shows short-lived rises in LH/FSH/E2 that help reproductive tract maturation, then axis quiets under central inhibition.

Puberty

- Initiation requires adequate **energy signals (leptin)** and maturational changes in **kisspeptin/NKB** signalling.
- Pulsatility appears first at night, then daytime. Early cycles post-menarche are often **anovulatory** until positive feedback fully matures.

Reproductive years

- Stable interaction of pulses and feedback produces regular ovulatory cycles (typically 24–38 days).

Lactation

- Suckling inhibits tuberoinfundibular **dopamine**, increasing **prolactin**; prolactin suppresses GnRH pulses → **lactational amenorrhoea**. **Oxytocin** mediates milk ejection but does not drive the amenorrhoea.

Pregnancy

- **hCG** rescues the corpus luteum early; placenta later dominates **E2/P4** production. High steroids keep GnRH/LH/FSH low. Pituitary lactotrophs hypertrophy, preparing for lactation.

Perimenopause and menopause

- Follicular depletion → low **inhibin** and E2 → **high FSH/LH** (FSH > LH). Thermoregulatory instability and **KNDy neuron** plasticity contribute to vasomotor symptoms.

---

5) Modifiers of the HPO Axis

Prolactin

- Chronic elevation (prolactinoma, hypothyroidism via ↑TRH, dopamine-antagonist drugs, chest wall lesions) **inhibits GnRH** → oligo/amenorrhoea, galactorrhoea, infertility.

Thyroid hormones

- **Hypothyroidism**: ↑TRH → ↑prolactin; cycles may be anovulatory/menorrhagic.
- **Hyperthyroidism**: oligomenorrhoea; fertility may be reduced until euthyroid.

Adrenal and stress

- **Cortisol/CRH** suppress GnRH pulsatility. Chronic stress, acute illness and excessive exercise can produce **functional hypothalamic amenorrhoea (FHA)**.

Metabolic signals

- **Leptin** reflects energy sufficiency; **insulin** modulates ovarian steroidogenesis.
- **Obesity**: hyperinsulinaemia augments ovarian androgen production and lowers SHBG, contributing to **PCOS**.

- **Under-nutrition**: low leptin reduces GnRH pulse frequency (FHA).

Circadian and environmental factors

- Sleep deprivation, shift work and extreme endurance training alter **pulse timing** and can elongate cycles or cause anovulation.

---

6) Clinical Neuroendocrine Patterns

Functional Hypothalamic Amenorrhoea (FHA)

- **Triggers**: caloric deficit, stress, over-exercise.
- **Labs**: low/normal LH & FSH, low E2, normal prolactin/TSH; often low leptin.
- **Management**: restore energy balance, stress reduction; cyclic oestrogen–progestin for bone; fertility—with ovulation induction after lifestyle correction.

Hyperprolactinaemia

- **Causes**: micro/macroprolactinoma, hypothyroidism, antipsychotics, SSRIs, opioids.
- **Features**: amenorrhoea, galactorrhoea, headaches/visual symptoms (macroadenoma).
- **Treatment**: **cabergoline** preferred; treat hypothyroidism; pituitary MRI if marked elevation.

Polycystic Ovary Syndrome (PCOS)

- **Neuroendocrine hallmark**: relatively **rapid pulses** favour **LH**; hyperandrogenism and insulin resistance maintain follicular arrest.
- **Labs**: may show ↑LH/FSH ratio (not diagnostic), ↑testosterone; AMH often high.
- **Treatment**: lifestyle; **letrozole** for ovulation induction; metformin for metabolic indications; screen long-term cardiometabolic risk.

Primary Ovarian Insufficiency (POI)

- Age <40 with oligo/amenorrhoea, **high FSH/LH and low E2**.
- Aetiologies: autoimmune, genetic, iatrogenic.
- **Management**: hormone therapy for symptoms/bone; fertility via donor oocytes.

Thyroid disorders

- Correcting thyroid status often restores cycles.

Outflow obstruction vs neuroendocrine failure

- Primary amenorrhoea with **cyclical pain** suggests outflow obstruction (imperforate hymen, transverse septum), not HPO failure.

---

7) Investigations Based on Physiology

Baseline timing

- Day 2–5: **FSH, LH, E2** (interpret with cycle phase).
- **TSH**, **prolactin** (fasting morning if possible) at any time.
- **AMH**: any day for ovarian reserve.
- **Mid-luteal P4** (≈Day 21 for a 28-day cycle) confirms ovulation.

Dynamic tests (selected scenarios)

- **GnRH stimulation**: pituitary reserve (specialist use).
- **Progesterone challenge**: tests endometrial oestrogenisation and outflow.

Imaging

- **Pelvic ultrasound** for follicular tracking and PCOM morphology.
- **Pituitary MRI** for significant hyperprolactinaemia.
- **Thyroid ultrasound** only if nodules/goitre.

Pattern table

Condition	FSH	LH	E2	Prolactin	TSH	Pointer
FHA	Low/normal	Low/normal	Low	Normal	Normal	Low BMI/stress/exercise
Hyperprolactinaemia	Low/normal	Low/normal	Low	**High**	±High	Galactorrhoea, headache
PCOS	Normal	Normal/↑	Normal	Normal	Normal	Hyperandrogenism, anovulation
POI	**High**	High	**Low**	Normal	Normal	Age <40
Hypothyroid	Normal	Normal	Variable	**High**	**High**	Menstrual disturbance

8) Therapeutic Principles

- **Restore normal inputs**: nutrition, sleep, stress control, balanced exercise.
- **Cycle control and suppression**: combined oral contraceptives; **GnRH agonists/antagonists** for endometriosis/fibroids (with **add-back** to protect bone).
- **Ovulation induction**: **letrozole** first-line in PCOS; **gonadotropins** with monitoring if required; **hCG** to trigger ovulation.
- **Prolactin excess**: **cabergoline** (dopamine agonist); surgery rarely needed.
- **Thyroid**: normalise TSH.
- **POI**: hormone therapy and early fertility counselling; screen bone health.
- **Lactation**: explain physiological amenorrhoea; advise contraception if pregnancy not desired.

9) Integrative Note

Though framed in modern physiology, the clinical goals resonate with Ayurvedic emphasis on **ṛtuśuddhi** (cycle regularity), **ahara-vihara** balance, and control of **manasika nidāna** (stress). Situations like **atyāhāra-vyāyāma** (over-exercise) and **alpāhāra** (caloric deficit) parallel FHA, while **medoroga/prameha** terrain reflects the metabolic drivers of PCOS. Use these parallels to counsel patients holistically while applying precise neuroendocrine diagnostics.

10) Key Take-Home Revision

- **Pulsatile GnRH** encodes pituitary output; **continuous** exposure suppresses LH/FSH.
- **Sustained high oestrogen** triggers **LH surge** and ovulation.
- **Progesterone** slows pulses and secures the luteal phase.
- **Prolactin, thyroid, cortisol, leptin/insulin** can derail the axis.
- Interpret labs with **cycle phase** and clinical context; treat the **level of the lesion**.

Assessment

A) MCQs (one best answer)

1. The neuronal peptide that most directly stimulates GnRH neurons at puberty is:
   A. Dynorphin B. Kisspeptin C. CRH D. Vasopressin
   Answer: B
2. Continuous administration of a GnRH agonist for several weeks will:
   A. Increase LH and FSH secretion
   B. Suppress LH and FSH secretion
   C. Selectively increase FSH
   D. Have no effect
   Answer: B
3. The immediate endocrine event that triggers ovulation is:
   A. FSH plateau due to inhibin B
   B. LH surge following sustained high oestrogen
   C. Sudden fall of progesterone
   D. Rise of prolactin
   Answer: B
4. In the early follicular phase, selective suppression of FSH is largely due to:
   A. Inhibin A B. Inhibin B C. Activin D. Follistatin
   Answer: B
5. The primary reason for lactational amenorrhoea is suppression of:
   A. Aromatase in granulosa cells
   B. GnRH pulsatility by high prolactin
   C. LH receptor expression on theca cells
   D. Oxytocin release
   Answer: B
6. A 22-year-old runner with BMI 17, stress, and amenorrhoea shows low/normal LH & FSH, low E2, normal TSH and prolactin. Most likely is:
   A. PCOS B. POI C. FHA D. Hyperprolactinaemia
   Answer: C
7. In PCOS, the GnRH pulse pattern is typically:
   A. Slow pulses favouring FSH
   B. Rapid pulses favouring LH
   C. Continuous non-pulsatile
   D. Absent
   Answer: B
8. Postmenopausal gonadotropin pattern is:
   A. Low FSH, low LH
   B. High FSH, high LH
   C. High FSH, low LH
   D. Low FSH, high LH
   Answer: B
9. Which statement about progesterone is correct?
   A. It speeds up GnRH pulses
   B. It lowers basal body temperature
   C. It slows GnRH pulses and stabilises the endometrium
   D. It triggers the LH surge
   Answer: C
10. The best single explanation for positive feedback in the late follicular phase is:
    A. High oestrogen increases KNDy dynorphin
    B. High oestrogen induces preoptic surge centre activation
    C. High progesterone drives GnRH surge
    D. Low inhibin A removes FSH inhibition

Answer: B

B) Short Answer Questions (3–5 lines each)

1. Describe the KNDy neuron model of the GnRH pulse generator and the roles of kisspeptin, NKB and dynorphin.
2. Explain how sustained high oestrogen converts negative to positive feedback to produce the LH surge.
3. Outline the neuroendocrine basis of hyperprolactinaemic amenorrhoea and its first-line treatment.
4. List the baseline hormonal tests for secondary amenorrhoea and justify their timing.
5. Contrast the neuroendocrine profiles of FHA and POI.

C) Long Answer Questions

1. **Describe** the HPO axis in detail, including anatomical pathways, GnRH pulsatility, pituitary response, ovarian feedback (oestrogen, progesterone, inhibin/activin/follistatin), and the surge mechanism. **Discuss** how this physiology changes during puberty, lactation and menopause.
2. **Discuss** PCOS and hyperprolactinaemia as disorders of neuroendocrine control: pathophysiology, laboratory/ultrasound findings, differential diagnosis, and first-line evidence-based management.

D) Case-Based (OSCE-style)

A 28-year-old woman with oligomenorrhoea, acne and BMI 32 has Day-3 labs: FSH 5 IU/L, LH 11 IU/L, E2 normal, prolactin normal, TSH normal; total testosterone elevated; AMH high.

- a) Identify the most likely diagnosis and the underlying neuroendocrine disturbance.
- b) State first-line ovulation induction and why it is preferred.
- c) Name two long-term metabolic risks and how you will screen them.