

Detailed Study Notes: Episode 459

Nicky Keay, MB BChir – Hormones & Healthspan

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Introduction to this Episode

The endocrine system plays a central role in growth, development, metabolism, reproduction, and physical well-being throughout life. Hormones interact in complex networks, orchestrating a range of critical functions. Over the lifecourse we experience a variety of changes in hormone levels, fluctuations, patterns and actions. Additionally, lifestyle factors and disease processes can impact the levels and functions of hormones.

In this episode Dr. Nicky Keay, a medical doctor with expertise in the field of exercise endocrinology, is on the podcast to discuss a variety of endocrine related issues, including: hormone diurnal variation, bone health, amenorrhoea, HRT, perimenopause, and thinking about hormones and aging.

Connection to Previous Episodes

- Dr. Keay was previously on the podcast in [episode 357](#), discussing: Female hormone profiling, how the menstrual cycle impacts risk of injury and performance, tracking the menstrual cycle, and Relative energy deficiency in sport (RED-S).
- Dr. Kirsty Elliot-Sale, Professor of Female Endocrinology and Exercise Physiology at Manchester Metropolitan University, was on the podcast in [episode 280](#) discussing menstrual disorders, energy availability, screening and diagnosis of RED-S, and recommendations for at-risk athletes.
- In [episode 445](#), Dr. Hazel Wallace discussed the impact of menstrual cycle phase on cravings, functional hypothalamic amenorrhea and the physiological changes at menopause.
- In [episode 402](#) Prof. Leanne Redman discussed the intergenerational transmission of obesity and the impact on the fetus of prolonged exposure to excess glucose and triglycerides in the mother.
- In [this written Sigma Statement](#) we provide a lifespan overview of nutritional considerations for females. We discussed iron-deficiency anaemia, PCOS, the peri-menopausal lifestage and more.

Pituitary Axes

The profiles of pituitary hormones provide a key insight into regulation of the endocrine system across the human lifespan. The profiles of hormones of the major pituitary axes across the lifespan are distinct, although all are subject to different configurations of feedback regulation.

Some of the main axes:

- Hypothalamic-pituitary-adrenal axis
- Hypothalamic-pituitary-thyroid axis
- Hypothalamic-pituitary-testicular axis

Hypothalamic-pituitary-adrenal axis

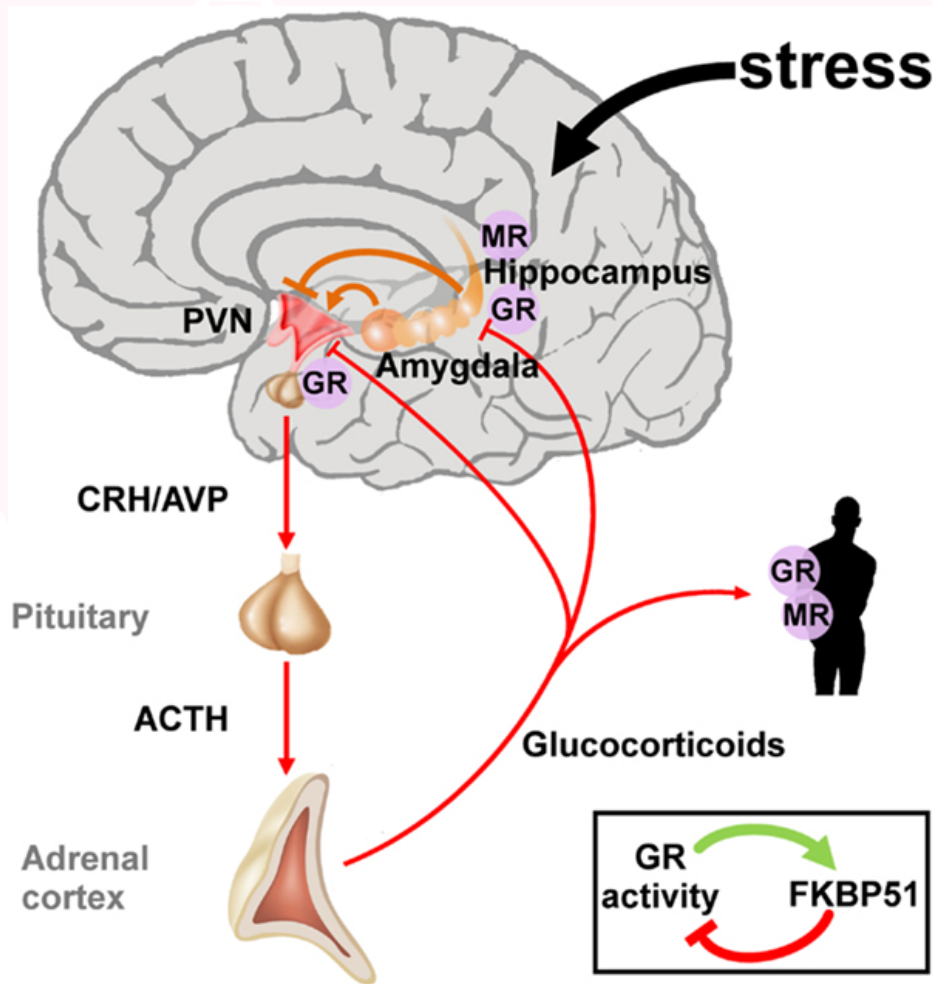
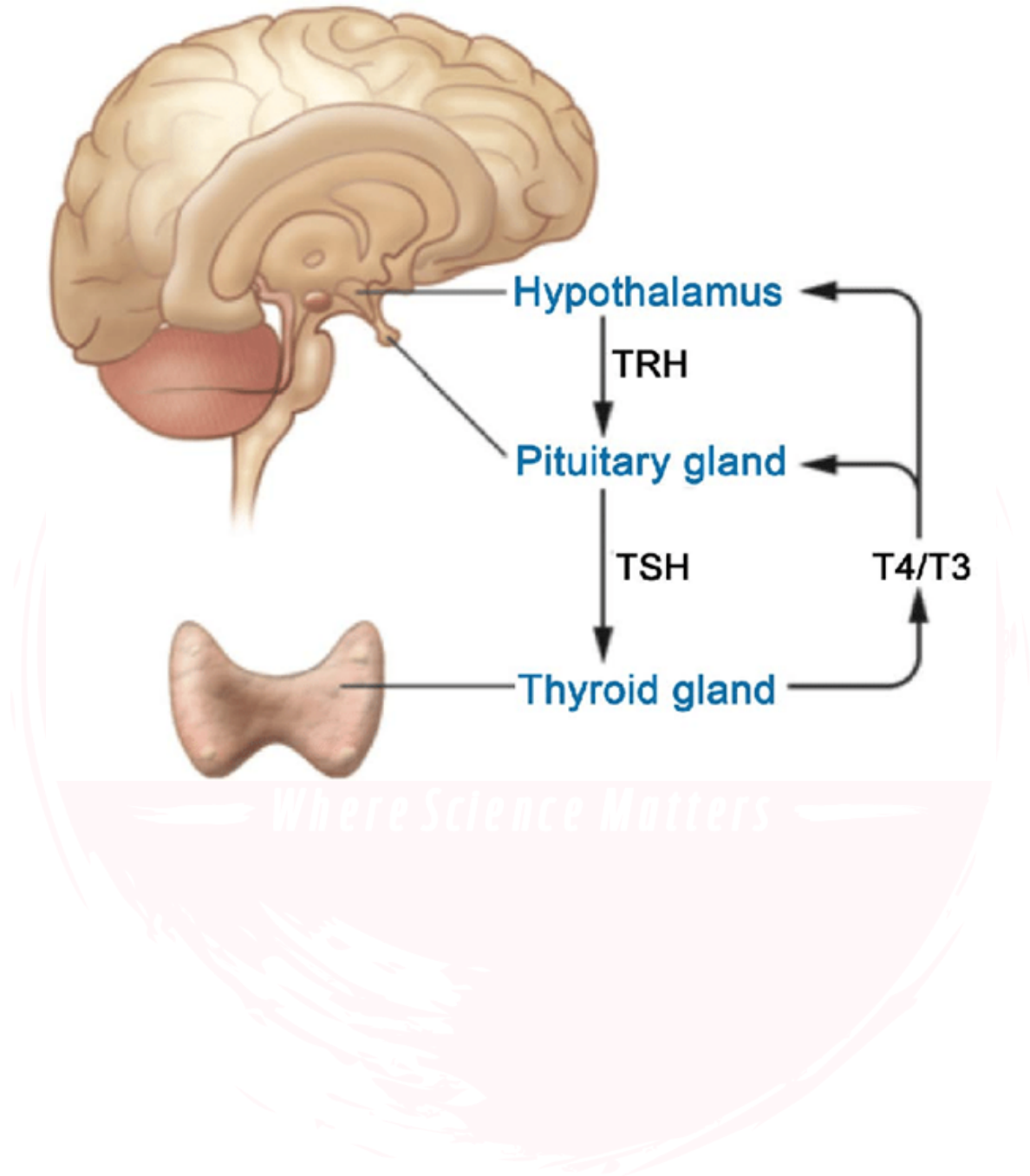
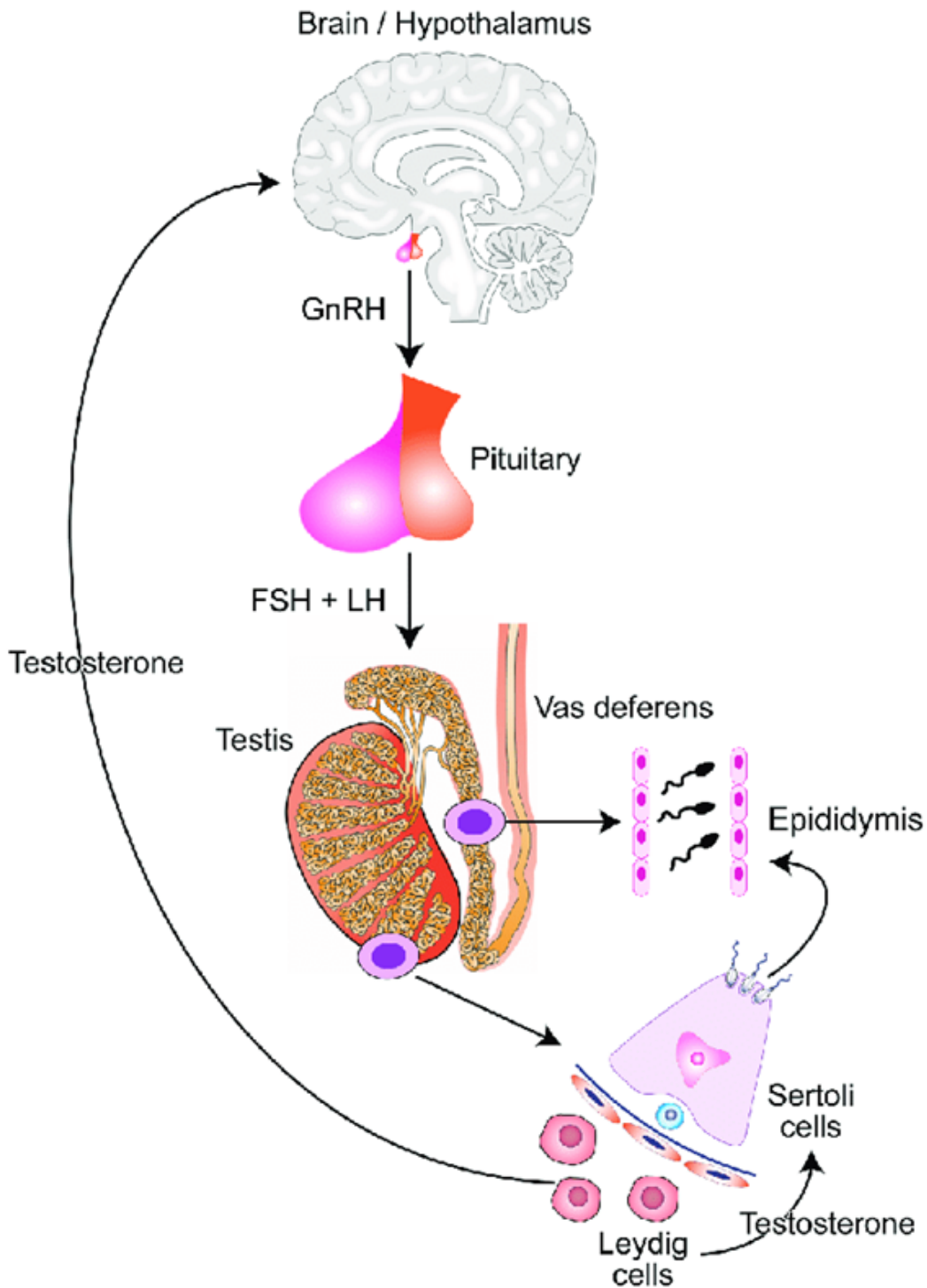


Image from: [Raabe & Spengler, Front Psychiatry, 2013 Aug 7:4:80](#)

Hypothalamic-pituitary-thyroid axis



Hypothalamic-pituitary-testicular axis



The hypothalamic-pituitary-testicular axis and its role in spermatogenesis. CCBY 4.0 Licence - John Reynolds-Wright. [Image here](#).

Fetal Factors & the Maternal Environment

- Both the status and the profile of hormonal axes can be shaped differently at birth based on the maternal environment and fetal factors.
- Hormones play a central role in regulating fetal growth and development. They act as maturational and nutritional signals in utero and control tissue development and differentiation according to the prevailing environmental conditions in the fetus.
- The insulin-like growth factor (IGF) system plays a critical role in fetal and placental growth throughout gestation ([Giquel & Le Bouc, 2006](#)).
- During pregnancy, an adverse maternal hormonal environment can potentially lead to problems for the fetus, with possibly the most important being the potential for abnormal fetal brain development.
- In relation to this maternal hormonal environment, the thyroid hormones and cortisol have been the most frequently studied hormones over the last number of years. However, it seems that there are also several others that could influence fetal neurodevelopment and other health outcomes.

The relative concentrations of maternal cortisol and free thyroid hormones during pregnancy:

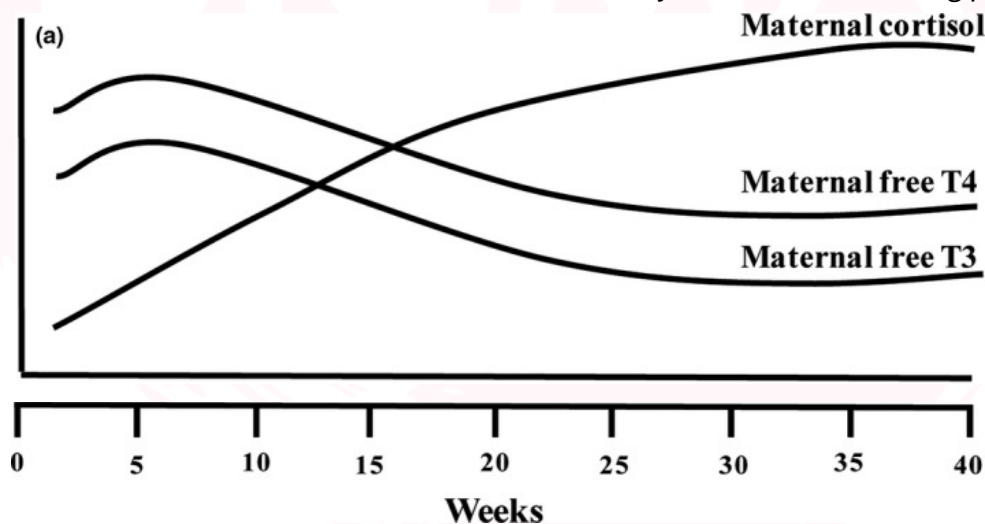


Figure from: [Miranda & Sousa, Brain Behav. 2018 Jan 24;8\(2\):e00920](#)

Time-specific actions of HPA and HPT axes on fetal brain development:

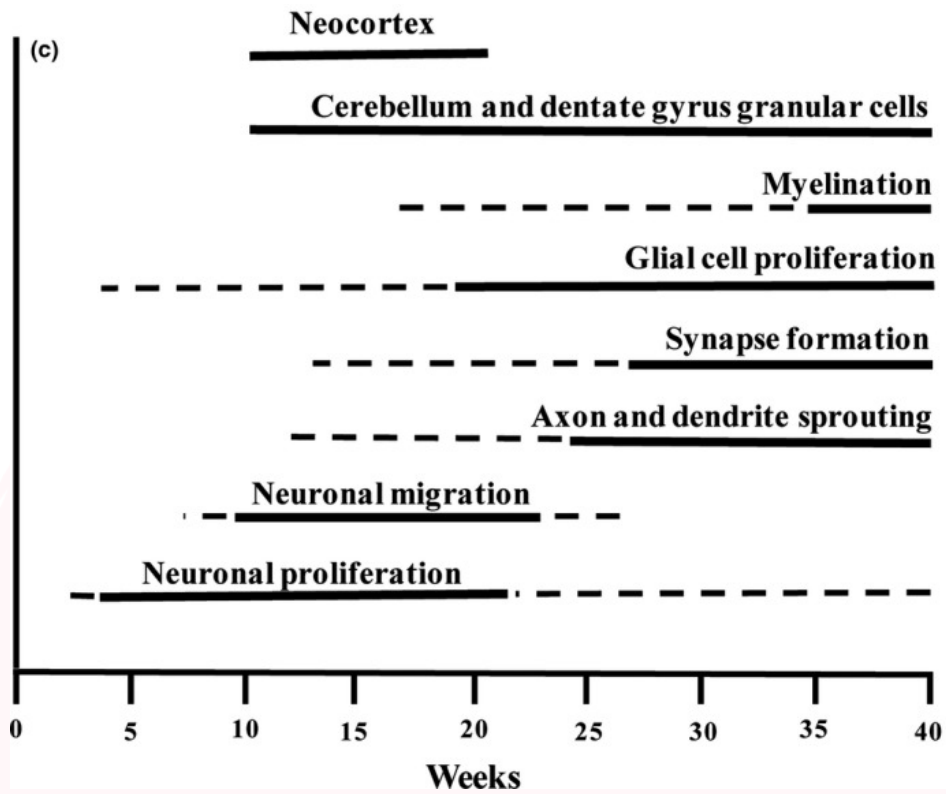


Figure from: [Miranda & Sousa, Brain Behav. 2018 Jan 24;8\(2\):e00920](#)

Hormone Cycles, Diurnal Variation & Circadian Effects

Rhythms in biology:

- Different rhythms based on duration:
 - Ultradian rhythm = lasting less than 24 hours
 - E.g. Sleep occurs in several repetitive cycles of ~90 minutes.
 - Infradian rhythm = lasting more than 24 hours
 - E.g. The menstrual cycle has an approximate cycle length of ~28 days that repeats.
 - Circadian rhythm = a rhythm of about 24 hours
- Some hormones that occur with a circadian rhythmicity include melatonin, cortisol and leptin.
- There is evidence that circadian misalignment can cause increased appetite via increases in ghrelin ([Qian et al., 2019](#)).

The normal synchronous relationships between sleep and daytime activity and cortisol, melatonin and body temperature:

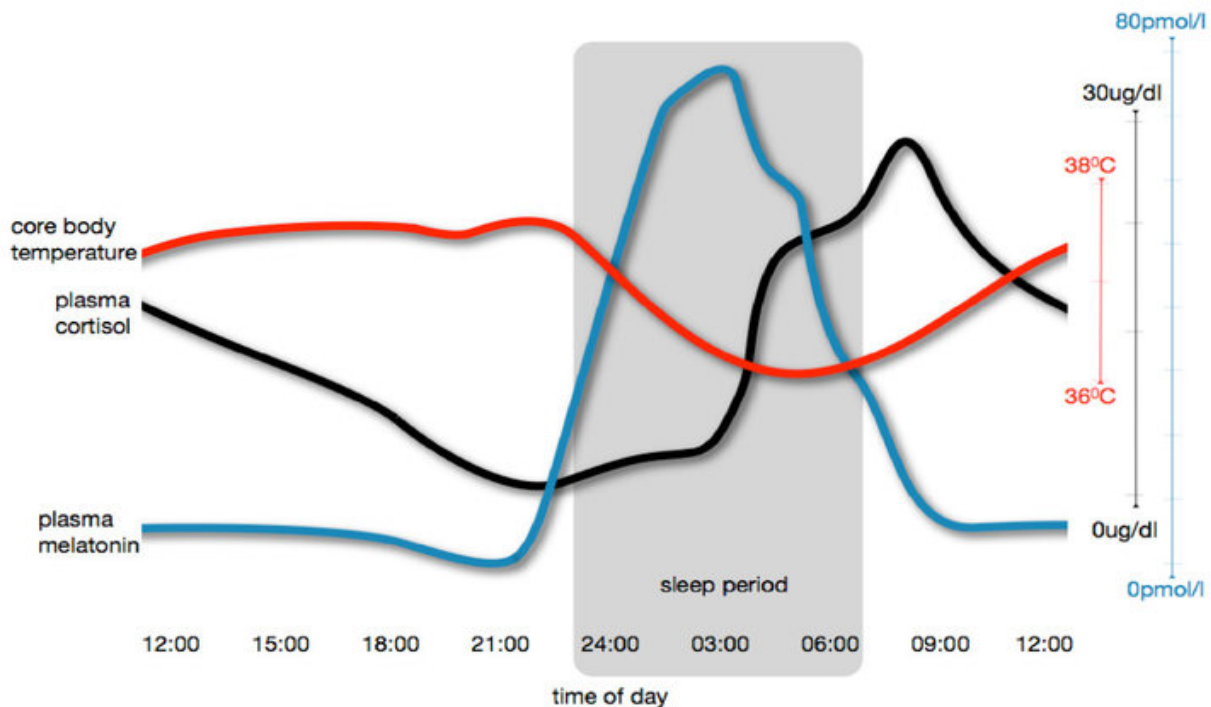
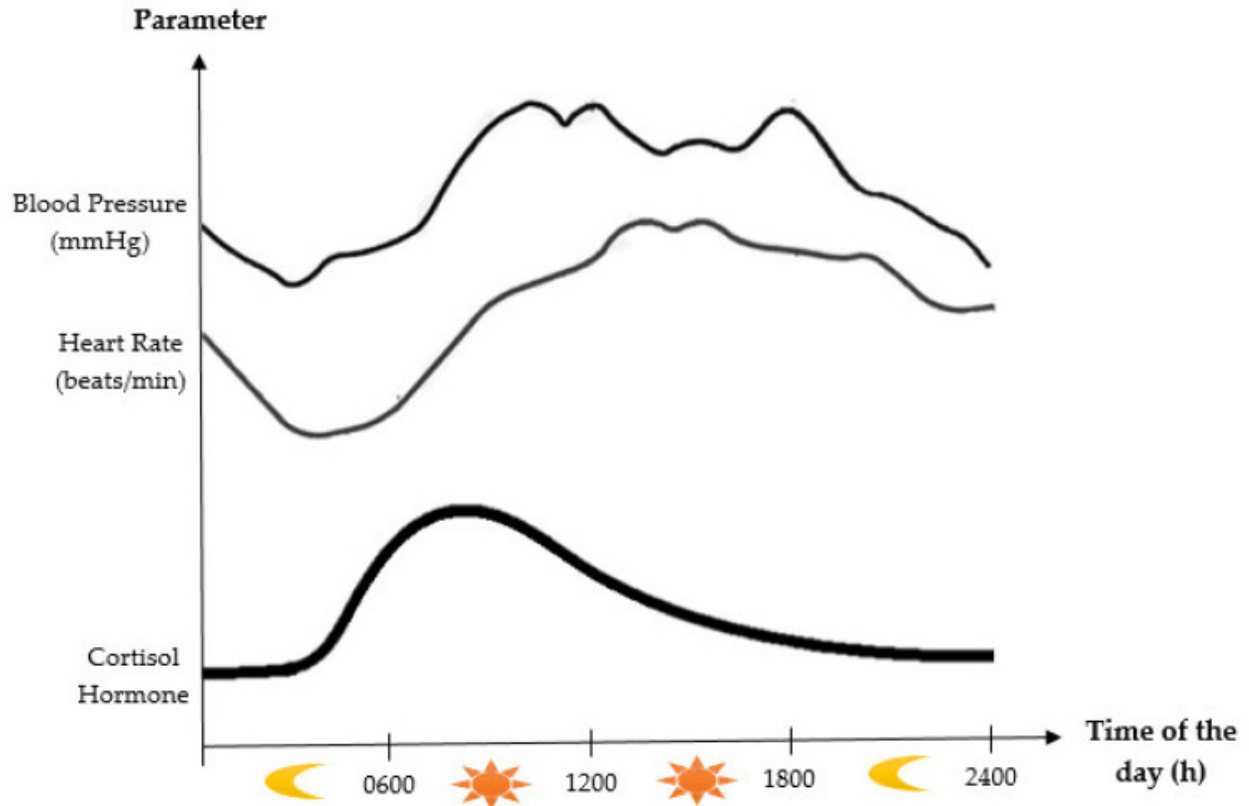


Image from: [Hickey et al., BMC Med. 2013 Mar 22;11:79.](#)

Diagram showing the circadian rhythms of blood pressure, heart rate, and cortisol:

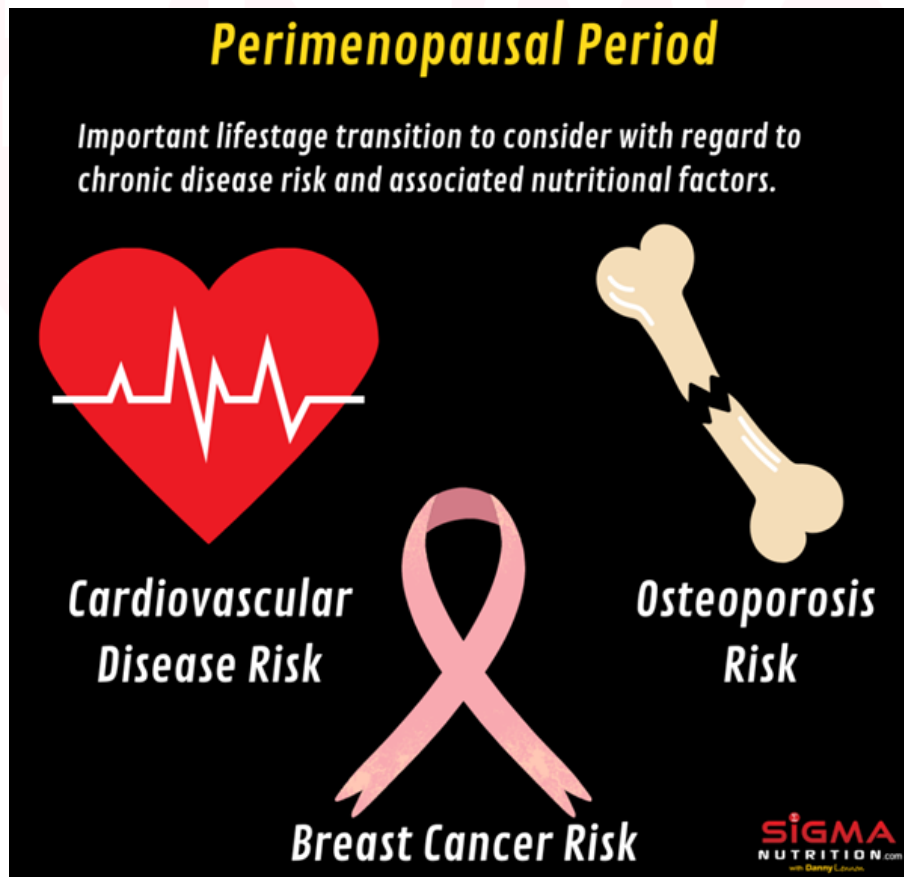


From: [Amzi et al., Int J Environ Res Public Health. 2021 Jan 14;18\(2\):676](#)

- Because hormone profiles have a rhythmicity (that is unique for each hormone and axis), this has implications for measurement.
- For example, a single hormone measure may reflect the time of time or time of the menstrual cycle, rather than an actual pathological elevation/suppression of a hormone.

Peri-menopause

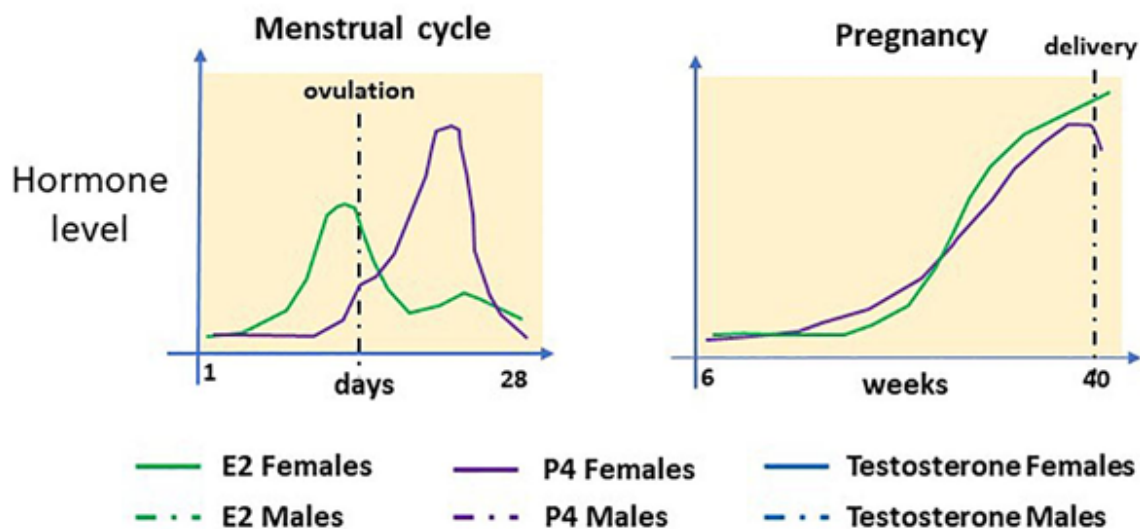
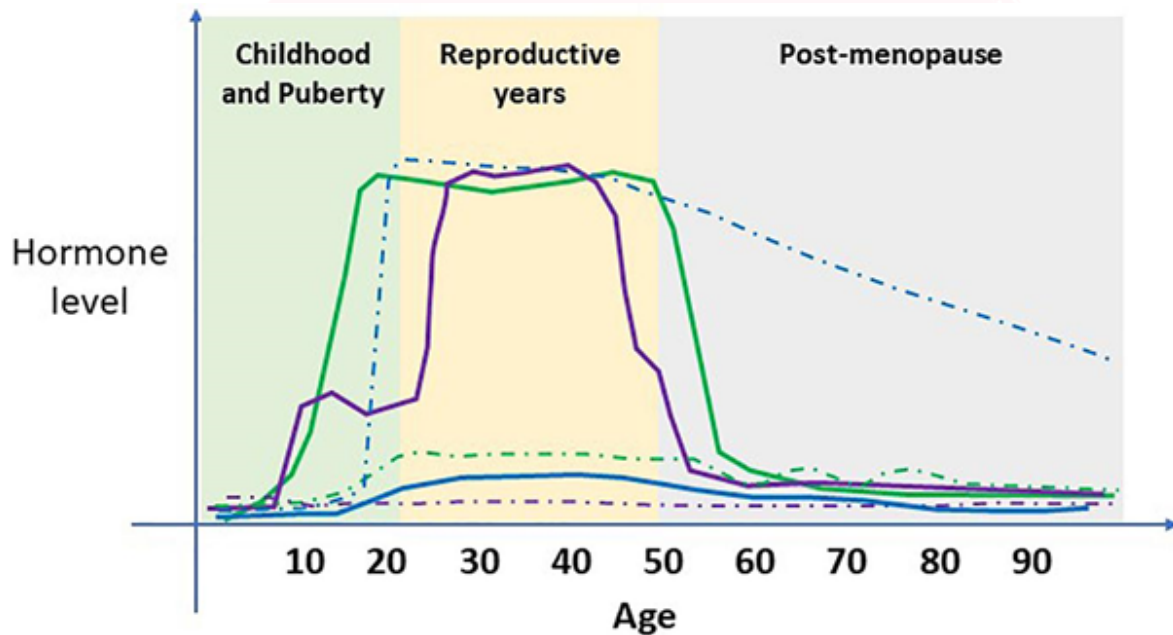
- Menopause is defined as not having periods for 1 year.
- So menopause is a retrospective diagnosis.
- Perimenopause is the transition from having regular periods, with associated characteristic fluctuations of female hormones over the menstrual cycle, to the situation of menopause.
- The perimenopausal period represents an important life stage with regard to chronic disease risk and associated nutritional factors:
 - With increased life expectancy in the developed world, women may spend up to 30 years or more in the post-menopausal phase.
- In particular, this is a life stage where three areas of health should take a focus, particularly when it comes to diet and lifestyle:
 - Cardiovascular disease
 - Breast cancer risk
 - Osteoporosis
- For more on these issues, you can read [this Sigma Statement](#).



Hormone Changes Over Time

The image below shows serum concentrations of sex steroid hormones. Specifically:

- In females, Estrogen and Progesterone are the predominant hormones.
 - Concentrations increase at puberty, undergo cyclical changes during the menstrual cycle and steadily increase during pregnancy.
 - At menopause, concentrations decline to pre-puberty levels.
- Testosterone is the predominant male hormone.
 - Increases at puberty. Remains high until late in life when levels decline steadily.



— E2 Females — P4 Females — Testosterone Females
- - - E2 Males - - - P4 Males - - - Testosterone Males

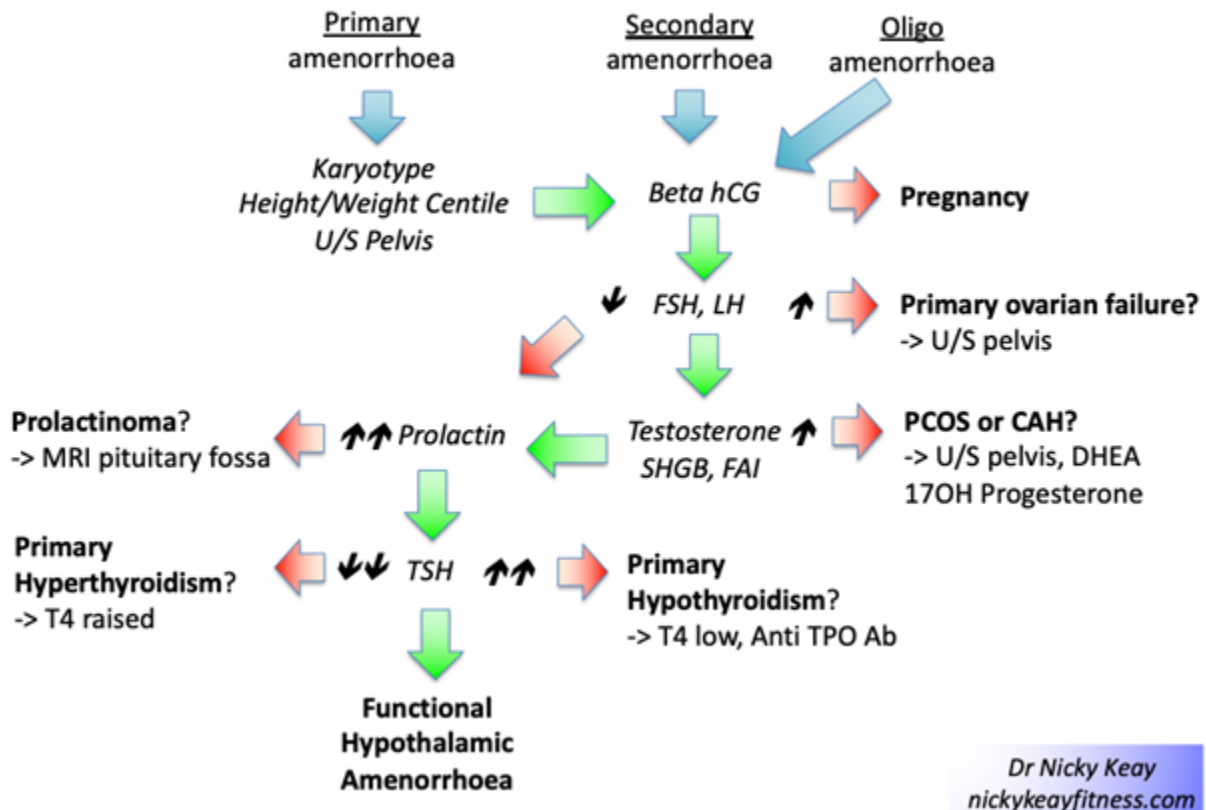
E2 = Estrogen (specifically estradiol); P4 = Progesterone; T/DHT = Testosterone

From: [Wray & Arrowsmith, Front Physiol. 2021; 12: 627260.](#)

Amenorrhoea

- Amenorrhoea is a clinical sign, not a diagnosis.
- After excluding pregnancy, the cause of amenorrhoea is identified based on follicle stimulating (FSH) and luteinising hormone (LH) levels, in keeping with WHO criteria.

Functional Hypothalamic Amenorrhoea: a diagnosis of exclusion



Via NickyKeayFitness.com:

Ovarian causes of amenorrhoea

- Raised FSH and LH in the presence of low estrogen suggests primary ovarian insufficiency (POI) in women who are under 40 years of age.
- Where FSH and LH are not unduly raised and estrogen is in range, or raised; in the presence of elevated testosterone, this is suggestive of polycystic ovary syndrome (PCOS).

Hypothalamic-pituitary causes of amenorrhoea

- Where FSH and LH are low range, together with low range oestradiol, prolactin should be scrutinized to exclude prolactinoma as the cause of hypothalamic amenorrhoea (HA).
- Before settling on a diagnosis of functional hypothalamic amenorrhoea (FHA), other endocrine causes of amenorrhoea should be considered, such as thyroid disorders. FHA is a diagnosis of exclusion.

FHA is where amenorrhoea is due to down regulation of the hypothalamic control of menstrual periods. FHA can be a presenting symptom of relative energy deficiency in sport (RED-S)

HRT in Menopause

- Hormone replacement therapy (HRT) improves both quality of life and reduces the risk of health issues in the long term such as cardiovascular disease (CVD) and osteoporosis.
 - CVD is the main cause of death in menopausal women.
- Titrating the type and dose of HRT for the individual women is very important.
- Body identical HRT
 - Offers many advantages.
 - This is HRT comprised of oestradiol and progesterone which are the identical molecular structure to those hormones that the ovaries produce.
 - Body identical HRT which is both licensed and regulated.
- “Bioidentical” HRT
 - Not advised
 - These forms of HRT are neither licensed nor regulated.