The endocrine system is made up of glands and tissues that produce hormones, the role of which is to coordinate and regulate vital functions in the human body. This seventh article of an eight-part series examines the anatomy and physiology of the testes and ovaries, as well as their role in producing a variety of steroid hormones that influence many diverse areas of human physiology. We also examine the endocrine role of the placenta and how placental hormones influence maternal physiology and help establish the maternal-foetal interface.

**Testes**

The testes are the primary male reproductive organs, responsible for spermatogenesis (sperm production) and the synthesis and secretion of the male sex hormone, testosterone. Unlike most other major organs, they are not protected in a body cavity, but reside in a specialised pouch of skin called the scrotum. This external location is essential because optimal spermatogenesis relies on maintaining the testes’ temperature at 32-35°C; this is 2-5°C cooler than the typical core body temperature of 37°C (Durairajanayagam et al, 2014). Each testis (testicle) is oval-shaped and, in adult males, is typically 4.5-5.1cm long and weighs 15-19g (Silber, 2018). The inner structural components are protected by an outer collagen-rich capsule called the tunica albuginea (Fig 1a). Internally, each testis is divided by septa into lobules containing tightly folded seminiferous tubules; these are the site of spermatogenesis.

**Spermatogonia**

Active dividing germinal cells of the testes, spermatogonia give rise to spermatocytes that are primarily located around the inner peripheries of the seminiferous tubules. Spermatogonia initially proliferate by normal cell division (mitosis) before undergoing a special type of cell division called meiosis, which halves the number of
Chromosomes from the diploid number of 46 to the haploid number of 23 (Knight and Andrade, 2018). As with ova in the ovaries (discussed later in this piece), the production of haploid gametes (sex cells) is essential to restore the diploid number of chromosomes when a haploid spermatozoan fuses with a haploid ovum during fertilisation (23 + 23 = 46).

**Sertoli cells**
Also called nurse cells, these large cells extend from the inner periphery into the lumen of the seminiferous tubules. These cells are vital to the growth, maturation and differentiation of spermatozoa, releasing a range of nutrients and growth factors necessary for normal sperm production (França et al, 2016).

**Leydig cells**
Also known as interstitial cells, these are associated with the outer periphery of the seminiferous tubules. Typically spindle (diamond) shaped, they form the major endocrine cell population of the testes. They take up cholesterol and use it to synthesise testosterone, the primary male sex hormone (Zirkin and Papadopoulos, 2018).

Testosterone is an anabolic steroid, largely responsible for the male secondary sexual characteristics that become apparent during puberty, including increased muscle mass, increased growth of body and facial hair, expansion of the larynx (voice breaking and deepening) and increased libido (sex drive). Testosterone has multiple effects on physiology (Table 1).

**Testosterone and ageing**
In most men, testosterone production begins to decline in their 30s by around 1-1.4% per year (Knight and Nigam, 2017). Known as the andropause, this often has noticably negative effects on male endocrine cell population of the testes. They take up cholesterol and use it to synthesise testosterone, the primary male sex hormone (Zirkin and Papadopoulos, 2018).

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**Ovaries**
These are the primary female reproductive organs located in the pelvic cavity. They

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**Table 1. Physiological effects of testosterone**

<table>
<thead>
<tr>
<th>Organ system/tissue</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal system</td>
<td>● Increased bone growth and bone density</td>
</tr>
<tr>
<td></td>
<td>● Increased risk of fracture if testosterone levels fall</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>● Increased spermatogenesis</td>
</tr>
<tr>
<td></td>
<td>● Increased size of testes, penis, prostate gland and seminal vesicles</td>
</tr>
<tr>
<td>Nervous system</td>
<td>● Increased libido</td>
</tr>
<tr>
<td></td>
<td>● Enhanced cognitive skills when elevated (either naturally or through use of anabolic steroids)</td>
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<tr>
<td></td>
<td>● May be associated with increased aggression</td>
</tr>
<tr>
<td></td>
<td>● Low levels associated with reduced libido, low mood and increased anxiety</td>
</tr>
<tr>
<td>Muscle</td>
<td>● Powerful anabolic effects with enhanced muscle growth</td>
</tr>
<tr>
<td></td>
<td>● Low levels associated with muscle atrophy (sarcopenia) and increased weakness/frailty</td>
</tr>
<tr>
<td>Skin</td>
<td>● Increased skin thickness</td>
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<tr>
<td></td>
<td>● Reduced subcutaneous fat</td>
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<tr>
<td></td>
<td>● Growth of body and facial hair</td>
</tr>
<tr>
<td></td>
<td>● Increased sebum production and predisposition to acne</td>
</tr>
<tr>
<td></td>
<td>● Potential for male pattern baldness in some men</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>● Expansion of the larynx and deepening of voice at puberty</td>
</tr>
<tr>
<td>Cardiovascular system and blood</td>
<td>● Enhances cardiovascular function</td>
</tr>
<tr>
<td></td>
<td>● Reduces triglycerides and improves cholesterol profile</td>
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<tr>
<td></td>
<td>● Increases erythropoiesis (production of red blood cells), enhancing oxygen transport</td>
</tr>
<tr>
<td></td>
<td>● Low levels associated with increased risk of coronary artery disease</td>
</tr>
</tbody>
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**Fig 1. Testis and seminiferous tubule structure**

![Diagram of testis and seminiferous tubule structure](image-url)
produce haploid ova (oocytes), which develop in fluid-filled sacs called follicles (Fig 2). Each mature ovary is an irregular, lumpy, almond-shaped structure, typically 3-5cm long and weighing around 5-8g (Wallace and Kelsey, 2004). The developing, and subsequently degenerating, follicles form the primary endocrine tissue in the ovaries that synthesises and secretes oestrogens and progesterone.

**Menstrual cycle**
The menarche (first episode of menstruation) marks the onset of puberty in females; the current average age of the menarche worldwide is around 12 years (Canelón and Boland, 2020). Most women’s menstrual cycle lasts around 28 days – the term ‘menstrual’ is derived from the Latin mensis, meaning ‘monthly’. In reality, the menstrual cycle is comprised of two cycles – the ovarian cycle and the uterine cycle – which are closely interrelated.

**Ovarian cycle**
The ovarian cycle is the series of cyclical monthly events of follicle development and degeneration occurring in the ovaries. This consists of three distinct phases:

- **Follicular phase**
- **Ovulation** (typically around day 14);
- **Luteal phase**.

**Follicular phase**
In this phase, gonadotrophin-releasing hormone (GnRH) is released from the hypothalamus, initiating the release of follicle-stimulating hormone (FSH) from the anterior pituitary gland. FSH is a small peptide hormone that circulates in the blood and acts on the immature follicles in the ovaries. As its name implies, FSH stimulates the follicle to develop and enlarge (Orlowski and Sarao, 2021).

As the follicle grows and expands, it begins to release oestrogens (predominantly oestradiol) into the blood, with expanding follicular size correlating to increased oestrogen secretion. Gradually a fluid-filled space called the antrum develops in the follicle, increasing the pressure inside – this is known as a Graafian follicle, which is a mature follicle containing a haploid ovum (Fig 2).

**Ovulation**
GnRH from the hypothalamus initiates the release of luteinising hormone (LH) from the anterior pituitary gland. It is LH that initiates ovulation, with a further increase in pressure causing the ovarian follicle to rupture, propelling the ovum into the adjacent fallopian tube. Ovulation is a somewhat violent event, causing around 20% of women to experience a twinge of acute abdominal pain known as mittelschmerz (German for ‘middle pain’). It is important that nurses are aware of this, as mittelschmerz can be mistaken for the symptoms of appendicitis (Durai and Ng, 2009).

Following ovulation, the remnants of the follicular walls collapse to form the corpus luteum (yellow body), which is where LH gets its name – by triggering ovulation it indirectly leads to the formation of the corpus luteum (Fig 2).

**Luteal phase**
Here the corpus luteum is active, with the collapsed follicular walls beginning to secrete the female sex hormone, progesterone. Progesterone’s name indicates its function in helping maintain pregnancy (pro-gestational hormone), primarily through maintaining the integrity of the endometrial (womb) lining. If fertilisation and implantation occurs, progesterone secreted by the corpus luteum helps maintain the endometrial lining for around the first 10 weeks’ gestation until the placenta takes over, secreting progesterone for the remainder of the pregnancy (Kumar and Magon, 2012).

In most months, a pregnancy will not occur and the corpus luteum degenerates and shrinks into a small piece of scar tissue called the corpus albicans (Fig 2), reducing progesterone secretion and depriving the endometrium of its hormonal support. As a result, the blood vessels supplying the endometrial lining go into spasm, reducing blood flow to the endometrium. Gradually the cells of the endometrium die off, releasing internal enzymes that cause autodigestion of the functional layer, which is shed during menstruation (Bergeron, 2000).

**Uterine cycle**
This is the series of changes the endometrium undergoes during each 28-day cycle. Like the ovarian cycle, it has three phases:

- **Menstrual phase** (day 1-5) – the endometrium is deprive of progesterone, causing breakdown and shedding of the endometrial lining;
- **Proliferative phase** (day 6-14) – the endometrial lining is rebuilt and begins to thicken and mature. This is primarily driven by the oestrogens secreted by the developing ovarian follicles (Orlowski and Sarao, 2021);
- **Secretory phase** (day 14-28) – as the new endometrial lining matures, progesterone secreted by the corpus luteum stimulates the endometrium to secrete a sticky mucoid material called uterine milk (Burton et al, 2007). This coats the surface of the endometrium, ensuring it is adherent, which encourages a fertilised ovum (zygote) to stick to it, helping implantation. The term ‘uterine milk’ is appropriate, as it can provide nutrition before implantation (Jones et al, 2015).

**Perimenopause and menopause**
Before the menopause, hormones regulating the ovarian and uterine cycles start to fluctuate, leading to progressively irregular cycles. This perimenopausal phase is highly variable in length, typically lasting between 2-10 years, and is associated with similar symptoms to the menopause itself. The average age at
which women experience the menopause is 50.7 years; it affects 95% of women aged 44-56 years (Knight and Nigam, 2017). Symptoms vary significantly, but commonly include hot flushes, vaginal shrinkage and dryness, reduced bone density, sleep disturbances, mood changes and depression – mostly due to reduced levels of circulating oestrogens and progesterone. Many women are afforded relief through hormone replacement therapy, which replaces either oestrogen alone or both oestrogen and progesterone.

**Hypothalamic-pituitary-gonadal axis**

The release of hormones from the testes and ovaries is governed by the hypothalamic-pituitary-gonadal (HPG) axis (Fig 3). The levels of testosterone and oestrogen are continually monitored by the hypothalamus and, when they begin to fall, GnRH is released from the hypothalamus into the hypothalamic portal circulation. GnRH stimulates secretion of FSH and LH from the anterior pituitary into the systemic circulation (Dwyer and Quinton, 2019).

In females, FSH stimulates the enlargement of ovarian follicles, which then begin secreting oestrogen, while in males it stimulates spermatogenesis (Santi et al, 2020). LH in females stimulates ovulation; in males, it stimulates the Leydig cells to synthesise and secrete testosterone (Nedresky and Singh, 2020). As the levels of circulating oestrogen and testosterone are monitored in real time by the hypothalamus, rises in oestrogen in females and testosterone in males leads to reduced GnRH secretion from the hypothalamus; this subsequently reduces secretion of FSH and LH by the anterior pituitary.

**Endocrine role of the placenta**

In the first week after fertilisation, the zygote formed from the fusion of spermatozoan and ovum undergoes repeated cell divisions, resulting in a tiny hollow ball of blastodermic cells known as a blastocyst. The blastocyst consists of two major regions:

- Inner cell mass, which develops into the embryo (baby);
- Trophoblast, which develops into the placenta.

The placenta is a transient organ, only present for the length of the pregnancy, during which time it forms an essential bridge between the maternal and foetal circulations. The average fully formed human placenta weighs around 500g and is usually disc shaped; it is typically 22cm in diameter and 2.5cm thick (Burton and Fowden, 2015). It functions as a barrier to prevent the direct mixing of maternal and foetal blood, while simultaneously facilitating the efficient movement of:

- Oxygen and nutrients from the maternal to the foetal circulation;
- Waste products from the foetal to the maternal circulation (Burton and Fowden, 2015).

The placenta acts as a major endocrine organ throughout pregnancy, and generates several key hormones essential for a healthy gestational period and successful delivery, as described below.

**Human chorionic gonadotropin**

Human chorionic gonadotropin (hCG) is the hormone detected in urine and blood-based tests to confirm pregnancy. A peptide hormone, it comprises 237 amino acids and shows some structural similarities to FSH and LH. Produced and secreted by trophoblast-derived cells, hCG enhances the production of progesterone from the corpus luteum until the placenta develops sufficiently and takes over. It also stimulates angiogenesis (growth of new blood vessels) in the endometrium and is thought to modulate immune responses at the maternal/embryonic interface, allowing maternal tolerance of the developing embryo and subsequent foetus (Nwabubii et al, 2017).

**Progesterone**

The production of hCG begins to wane around 6-8 weeks into pregnancy, so hCG stimulation of the corpus luteum declines. At this time, progesterone production gradually switches to the placenta, which becomes the major producer at around 10 weeks and remains so for the duration of the pregnancy (Kumar and Magon, 2012). Placental cells continually take up cholesterol from the maternal blood and this is used as the substrate to produce increasing amounts of progesterone; levels peak during the final four weeks of pregnancy, then decline after the delivery of the baby and placenta (Costa, 2016).

In addition to its key role in preventing endometrial breakdown, progesterone also:

- Inhibits uterine contraction;
- Helps ensure maternal immunotolerance of the foetus;
- Enhances proliferation of epithelial tissue in the breasts to prepare them for lactation;
- Enhances appetite during pregnancy to encourage additional caloric intake (Costa, 2016).
Clinical Practice
Systems of life

Leptin
Leptin is a peptide hormone consisting of 167 amino acids that has multiple physiological effects. As most leptin is secreted from fat cells (adipocytes), it is often referred to as an adipokine.

Leptin is important in regulating food intake; it is a satiety hormone that binds to receptors in the regions of the brain controlling appetite, where it reduces sensations of hunger. The placenta produces large amounts of leptin during pregnancy and it is suggested that, in some women, this may be associated with the nausea in morning sickness (Aghoozi et al., 2018).

As levels of leptin increase and peak in the second trimester of pregnancy, a tolerance to it can be established; this leads to increased food intake as it becomes less potent at suppressing hunger. Leptin tolerance is thought to be useful as it encourages increased calorific intake to prepare the body for the final stages of pregnancy and breast feeding (Ladymen et al., 2010).

Human placental growth hormone
Human placental growth hormone (hPGH), also known as growth hormone 2 (GH2), is structurally and functionally similar to the somatotropin (growth hormone) produced by the anterior pituitary. A peptide hormone, it consists of 191 amino acids that has multiple physiological effects. As blood volume increases by around 40-50% during pregnancy, relaxin – with progesterone and oestrogen – induces systemic vasodilation to accommodate this extra blood volume; this is usually accompanied by a characteristic drop in blood pressure in the second trimester of the pregnancy (Sanghavi and Rutherford, 2014).

Relaxin appears to work with progesterone to maintain endometrial integrity, particularly in early pregnancy, and stimulates cervical softening and ripening which are essential to the early stages of labour (Goldman and Weiss 2009).

In our final article in this series, we will examine the secondary endocrine functions of the kidneys, heart and skin.

References
France LR et al (2016) The Sertoli cell: one of the original fifty years of beauty and plasticity. Andrology; 4: 2, 189-212.

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