38 Anatomy and Physiology of the Female Reproductive System

Artemis Vogazianou

Contents

Abstract

At birth, a female baby already has her lifetime supply of oocytes that will be released through ovulation when she is sexually matured, between menarche and menopause. Puberty initially starts with thelarche (breast budding) around the age of 11 and menarche usually starts at an average age of around 13. Initial cycles are anovulatory, but subsequently a single egg is released each cycle during a woman's fertile years. The menopause is the end of menstrual cycles. Puberty, menstrual cycles, and establishment of pregnancy are controlled by the hypothalamic, pituitary, and ovarian hormones. Following the menopause, the ovaries are no longer able to produce enough oestrogen and ovarian failure results in a rise in the gonadotropins.

A. Vogazianou (✉)
Department of Diabetes and Endocrinology,
University College Hospital, London, UK
e-mail: artemisvogazianou@nhs.net

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_38

Keywords
Female reproduction · Puberty · Menstrual cycle · Ovulation · Menopause · Pregnancy Menarche · Thelarche · Tanner Stages

Abbreviations

17-OHP	17-Hydroxyprogesterone
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
FSH	Follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
IGF-1	Insulin-like frowth factor-1
IHH	Idiopathic hypogonadotropic hypogonadism
IVF	In vitro fertilisation
KISS1	Kisspeptin
LDL	Low-density lipoprotein
LH	Luteinising hormone
LPD	Luteal phase deficiency
PCOS	Polycystic ovarian syndrome

Key Terms

- **Puberty:** the period of 2–3 years prior to menarche when secondary sexual characteristics begin to develop and the final and most substantial growth spurt occurs, with fusion of the epiphyseal plates.
- **Thelarche:** breast budding
- **Adrenarche:** the onset of androgen hormone release from the matured adrenals
- **Pubarche:** the development of pubic hair
- **Menarche:** first period
- **Climacteric:** the 6–7 years leading up to the menopause, when menstrual cycles tend to be irregular and anovulatory
- **Menopause:** last period

Key Points

- The female endocrine reproductive system relies on the relationship between the hypothalamus, pituitary, and ovaries.
- A female is born with a finite number of oocytes 300–400 of which will be released through ovulation during a woman's reproductive life.
- Puberty starts around the age of 11 with breast budding and it's complete around 2.5–3 years later with the onset of menarche (first period). Initial cycles are irregular and tend to be anovulatory.
- Pregnancy is maintained by hormones released by the corpus luteum and subsequently the placenta and have a wide range of functions, including immune suppression in the mother to prevent loss of the pregnancy through immune mediated response.
- Climacteric starts in the late 40s and lasts around 6–7 years. Menstrual cycles during this period are also irregular and tend to be anovulatory until the menopause (last period).

38.1 Introduction

The female reproductive system is controlled by hormones secreted by the hypothalamus, the anterior pituitary, and the ovaries, which interact with each other in a dynamic way. Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus in response to neuronal activity in the limbic region of the brain, which is predominantly influenced by emotional and sexual factors.

GnRH is a small polypeptide which regulates the release of gonadotropins: luteinising hormone (LH) and follicle-stimulating hormone (FSH), by the gonadotrope cells of the anterior pituitary gland. The gonadotropins are then released in short bursts every 1–4 h, stimulating cells in the ovaries to synthesise and secrete oestradiol and progesterone, which in turn promote and regulate menstruation and ovulation.

High concentrations of oestrogen and progesterone in the serum provide negative feedback to the hypothalamus and therefore inhibit further secretion of GnRH (Fig. 38.1). Please refer Chap. 12 in Part III for more details on the menstrual cycle regulation by FSH and LH and the hypothalamic-pituitary and gonadal feedback.

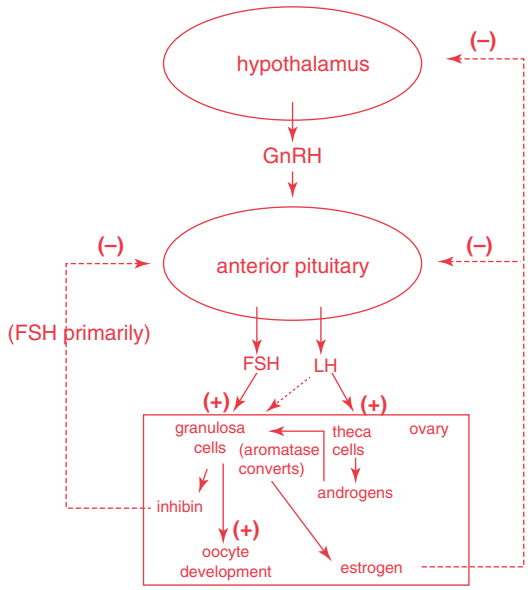

Fig. 38.1 The interplay between the hypothalamic, anterior pituitary, and ovarian hormones

GnRH released by the hypothalamus stimulates FSH and LH secretion by the anterior pituitary which in turn stimulates the secretion of oestrogen and progesterone by the ovaries.

FSH receptors only exist on the granulosa cell membranes of the ovaries and as the numbers of granulosa cells increase in late luteal phase, in parallel to increasing FSH levels, so does oestradiol secretion by granulosa cells, in response to FSH levels. The formation of LH receptors on the granulosa cells is stimulated by FSH, in the presence of oestradiol, facilitating these cells to also become responsive to LH and allowing secretion of small amounts of progesterone and 17-hydroxyprogesterone (17-OHP). These two hormones then have a positive feedback on the pituitary gland which has been primed by the high oestrogen levels to release LH.

FSH also stimulates the production of aromatase and 3β-hydroxysteroid dehydrogenase (3β-HSD). LH receptors are found on the theca cells of the ovaries, which produce androstenedione and small amounts of testosterone. Androstenedione is transported to the granulosa cells and converted into oestrone, by aromatase, and eventually converted to oestradiol by 17-β-hydroxysteroid dehydrogenase type I (17-β-HSD).

FSH also stimulates the secretion of inhibin from the granulosa cells, which suppresses FSH. There are two types of inhibin: *Inhibin B*, which reaches a peak in the early- to mid-follicular phase and has a second peak at ovulation and *Inhibin A*, which reaches its peak in the mid-luteal phase. Inhibin secretion is inhibited by GnRH and enhanced by insulin-like growth factor-1 (IGF-1).

Only unbound oestrogen and progesterone are biologically active, stimulating the target organs of the reproductive system (breasts, uterus, and vagina). However, most of the oestrogen and progesterone found in the bloodstream are bound to proteins. In general, oestrogen and progesterone inhibit the release of GnRH but around the time of ovulation stimulate gonadotropin secretion. Oestrogen and progesterone also have both direct and indirect effects on other major tissues including bone, skin, and muscle.

38.2 Ovarian Follicular Development

A female baby is born with a fixed number of germ cells (egg precursors). Germ cells begin as primordial oogonia that proliferate significantly by mitosis during the 3rd and 4th months of gestation of a female foetus. Around the same time, some oogonia begin to undergo meiosis, which halves the number of chromosomes to 23, resulting in the formation of haplotype primary oocytes. Beginning after the 4th month of gestation, oogonia and later oocytes are spontaneously lost by apoptosis, through a process called atresia. Eventually more than 99.9% of the original oogonia are lost by the time of birth.

The surviving germ cells (haplotype oocytes), become arrested in the meiotic prophase and are termed primary oocytes. By the 7th month of gestation, each viable primary oocyte develops a surrounding layer of granulosa cells, forming a primordial follicle. All primordial follicles, each containing its primary oocyte, potentially available for future reproduction during a woman's life are, therefore, present in the ovaries at birth. The so-called ovarian reserve is the number of oocytes or primordial follicles in a woman's ovaries at any given time, and this can be estimated by direct ultrasound visualisation or through measuring Mullerian hormone, with the latter being less reliable but often more widely used.

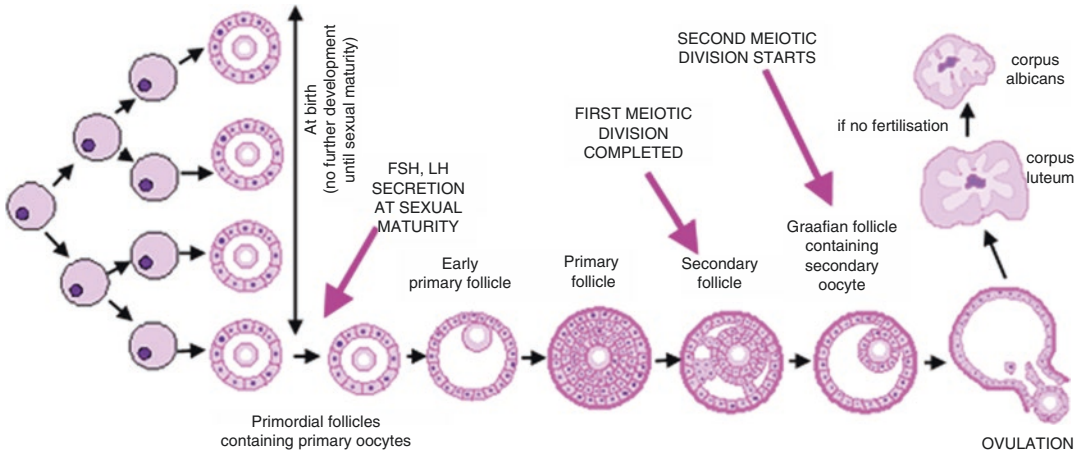

Fig. 38.2 Ovarian follicular development. Used with permission from Professor Michelle Peckham, Professor of Cell Biology, University of Leeds, School of Molecular and Cellular Biology, accessed via http://www.histology.leeds.ac.uk/female/FRS_ova.php

At birth, the ovary contains approximately 400,000 primordial follicles, with each one containing a primary oocyte. Primary oocytes do not undergo any further mitotic divisions and remain arrested in the **prophase** stage of **meiotic division I**, until after sexual maturity has been reached.

Following sexual maturity (completion of puberty), FSH and LH cause these primordial follicles to develop. In each ovarian cycle, FSH induces follicular growth in the ovaries and about 20 primordial follicles are activated to begin maturation and recruited for accelerated growth. Usually in each cycle, only one follicle fully matures and achieves ovulation (Fig. 38.2). This dominant follicle releases its oocyte at ovulation and promotes atresia of the other previously recruited follicles (please refer to ovulatory and luteal phases below for more details).

Over a woman's reproductive life, only ~300–400 eggs will be released, through ovulation.

38.3 Puberty

Puberty is the sequence of events that occur in order for a child to eventually sexually mature into an adolescent and eventually become an adult, acquiring adult physical characteristics and the capacity to reproduce. It is associated both with the development of secondary sexual characteristics, as well as rapid growth in height and weight.

Circulating LH and FSH levels are elevated at birth but fall to low levels within the first few months of life and remain low until puberty (see Fig. 38.7). The reproductive target organs undergo very few qualitative changes before the onset of puberty. While puberty primarily involves a series of physical transformations, the process can also have an effect on the psychosocial, behavioural and emotional development of the adolescent.

The mechanisms that initiate puberty are still not entirely clear. Central influences that regulate release of GnRH include neurotransmitters and peptides (e.g. gamma-aminobutyric acid [GABA] and kisspeptin [KISS1]). These and other factors may inhibit release of GnRH during childhood, but then initiate its release, to induce puberty in early adolescence (Watanabe et al. 2014; Zeydabadi Nejad et al. 2017).

Kisspeptin (KISS1), is a neuropeptide that acts upstream of GnRH-neurons and appears to be critical for maturation and function of the reproductive axis (Watanabe et al. 2014). Kisspeptins bind to and activate the G protein-coupled receptor, GPR54, located on the GnRH-neurons of the hypothalamus (Zeydabadi Nejad et al. 2017). Kisspeptin appears to be one of the

major activators of the GnRH-neurons and a prerequisite for the onset of puberty and maintenance of normal reproductive function. Abnormal KISS1/GPR54 system has been reported in both animal models and patients with certain forms of infertility, e.g. idiopathic hypogonadotropic hypogonadism (IHH) and polycystic ovarian syndrome (PCOS) (Zeydabadi Nejad et al. 2017; Seminara et al. 2003).

38.3.1 Age of Onset of Puberty

The timing of the onset of puberty is not completely understood and is most likely determined by a number of different factors. The age of onset of puberty varies amongst individuals and the rate of development through different stages is influenced by different factors. Over the last 150 years, the age at which puberty starts has been decreasing, primarily because of improved health and nutrition (Knudston and McLaughlin 2018; MedicineNET 2018). This trend has plateaued over the last few decades and occurs on average between the ages of 10 and 14 in girls (MedicineNET 2018).

Both environmental and genetic factors are involved in the onset of puberty. One theory is that reaching a critical weight or body-fat composition may be crucial, in the onset of puberty. It may be, that the overall earlier onset of puberty in the general population in recent years is related to the increase in childhood obesity (MedicineNET 2018).

Puberty appears to occur later than average in severely underweight and undernourished girls (Rosenfield et al. 2009). These observations suggest that there is a critical body weight or amount of fat necessary for the onset of puberty (Knudston and McLaughlin 2018; MedicineNET 2018; Soliman et al. 2014; Rosenfield et al. 2009), which may in turn vary between individuals or populations (Herman-Giddens et al. 1997).

Leptin, a hormone produced by the adipocytes, has been suggested as one possible mediator of the timing of puberty (MedicineNET 2018; Gueorguiev et al. 2001). In research studies, animals deficient in leptin, did not undergo puberty and administration of replacement leptin, resulted in restoration of puberty (Gueorguiev et al. 2001). Furthermore, girls with higher concentrations of leptin are known to have an increased percentage of body fat and an earlier onset of puberty than girls with lower levels of leptin. The concentration of leptin in the blood is known to increase just before puberty in both boys and girls.

Many other factors can influence the onset and progression of puberty. Genetic factors are also involved, as puberty occurs earlier in girls whose mothers underwent sexual maturity earlier. It has also been found that the onset of puberty also occurs earlier in girls who live in urban areas (Ameade and Garti 2016; Choudhary et al. 2016) and in blind girls (Flynn-Evans et al. 2009), but the underlying mechanisms for these observations are still unclear. The age of onset of puberty also varies amongst ethnic groups (Herman-Giddens et al. 1997) and it has been suggested that perhaps this is secondary to the mechanisms discussed above, i.e. genetic factors and body-fat composition.

38.3.1.1 Precocious Puberty

Precocious puberty is when a child enters puberty too early, often defined as before the age of 8 in girls and before the age of 9 in boys. It leads to the development of the secondary sexual characteristics because of increased sex steroid production, either because of aberrant gonadotropin stimulation or because of intrinsic disease of the ovaries or adrenals. The classic definition of sexual precocity is the appearance of secondary sexual characteristics before the age of 8 years in girls, but this cut-off may vary in ethnic minorities. The overall incidence of sexual precocity in America is estimated around 1:5000 to 1:10,000 with a female preponderance of around 10:1 (http://www.endotext.org). For more details, refer to the Chap. 4 in the Paediatric Part I of the textbook. Early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion is the most common mechanism and it is usually idiopathic but it can rarely be due to serious conditions such as hypothalamic tumours.

38.3.1.2 Pubertal Delay

The guidelines for initiating an evaluation of girls with pubertal delay are as follows (http://www.endotext.org):

- If there is no breast development by the age of 13 years
- If there is absence of menarche by the age of 14 years in the presence of hirsutism or if there is a history suggestive of an eating disorder or excessive exercise or an outflow abnormality
- If there is absence of menarche by the age of 15 years

These guidelines should be used in context of the patient circumstances and presentation.

In more than 90% of cases, delayed puberty is due to constitutional delay in growth and puberty. It, therefore, occurs in children who are otherwise healthy but have slower physical development than average. Typically, these children will be shorter than other children of the same age, they are often thin and there's a family history of delayed puberty. Sometimes delayed puberty and growth can be secondary to a chronic illness (e.g. Crohn's disease or cystic fibrosis), malnutrition (e.g. malabsorption), excessive exercise (e.g. competition athletes), or physical and psychological stress.

38.3.2 The Physical Changes of Puberty

Early in puberty, the hypothalamus becomes less sensitive to the inhibitory actions of oestrogen and progesterone on GnRH-release. This results in an increase in the release of GnRH, which in turn stimulates gonadotropin (LH and FSH) secretion. Gonadotropin secretion then stimulates production of the sex hormones, primarily oestrogen, which drives the development of secondary sexual characteristics.

Adrenarche occurs when a child's adrenal cortex starts to secrete adrenal androgen precursors and ultimately an increase in the production of the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS). Adrenarche occurs several years before the onset of puberty and is thought to stimulate pubic and axillary hair growth (Novello and Speiser 2018). DHEA, a weak androgen agonist, is the most abundant product of the adrenal cortex and is thought to be responsible for the clinical signs of pubarche (first appearance of pubic hair) by conversion to more potent androgens, testosterone, and dihydrotestosterone. DHEA becomes sulphated outside the adrenals to DHEAS, which is a stable marker for adrenal androgenic activity. Pubarche is the physical manifestation of androgenic hormone production and includes the development of pubic and axillary hair, adult body odour, and acne.

In general, there is a typical pattern in the physical changes that an individual undergoes during puberty, and the sequence of events tends to be fairly predictable (please refer to Chap. 4 in Paediatric Part I in the textbook). In most girls, the first sign of puberty is thelarche (breast budding) which is the beginning of breast development, and occurs at an average age of approximately 11 years. Pubic hair growth typically begins next, followed by the growth of axillary hair. However, in a minority of girls, pubic hair growth begins before breast development. The growth spurt tends to peak after the appearance of pubic and axillary hair.

Menarche (the onset of menstruation) usually happens after all the other physical changes and occurs approximately 2.5–3 years after the first signs of the onset of puberty. An underlying growth spurt also occurs in parallel to puberty, which peaks immediately before or around the time of the menarche. Body habitus changes, body fat increases and the pelvis and hips widen, partly due to accumulation of fat in the hips and thighs (Fig. 38.3). The growth spurt is limited after menarche, as the epiphyses fuse. Menstrual cycles are usually irregular at menarche and can take up to 5 years (average 2–3 years) to become regular.

The sequence of changes in puberty is referred to as the sexual maturity rating or Tanner stages, named after Tanner, a physician who in 1969 published a description of the sequence of physical changes that occur during

puberty (Figs. 38.3 and 38.4). The Tanner stages are determined by the development of secondary sex characteristics and encompass changes in the size and appearance of the external genitalia, the development of pubic hair, and breast development in girls from thelarche (breast budding) to adult female breast development. Tanner stages allow doctors to classify the extent of development of sex characteristics into five distinct steps ranging from stage 1 (pre-pubertal) to stage 5 (mature adult type) (Marshall and Tanner 1969; Novello and Speiser 2018).

Immediately after the start of menarche, there is a temporary period with anovulatory cycles. Several studies have shown this period of anovulatory cycles tends to be longer as the age at menarche increases (Hosokawa et al. 2012; Lee et al. 2013; Apter 1996). Therefore, girls who experience menarche before the age of 12 have a more rapid onset of ovulatory menstrual cycles than girls whose menarche started later (Apter 1996). Furthermore, studies have shown that 50% of adolescent girls whose first menstruation was after the age of 13 will not ovulate regularly over the next 4.5 years (MedicineNET 2018).

38.4 The Menstrual Cycle

Menstruation is the periodic discharge of blood and disintegrated endometrium, from the uterus through the cervix and vagina. It is caused by the rapid drop in progesterone and oestrogen levels secondary to reduced production from the ovaries, which takes place during each cycle if egg fertilisation, implantation, and pregnancy don't occur.

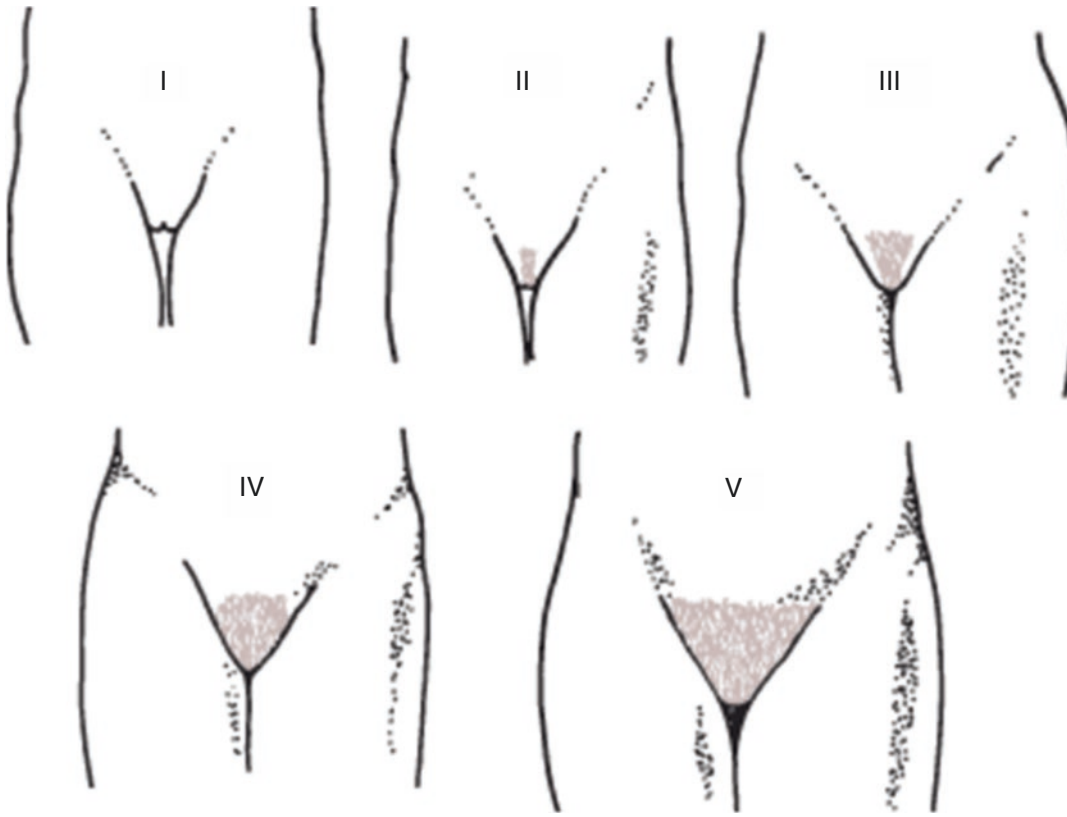

Fig. 38.3 The Tanner Stages I–V for pubic hair development in girls (Marshall and Tanner 1969)

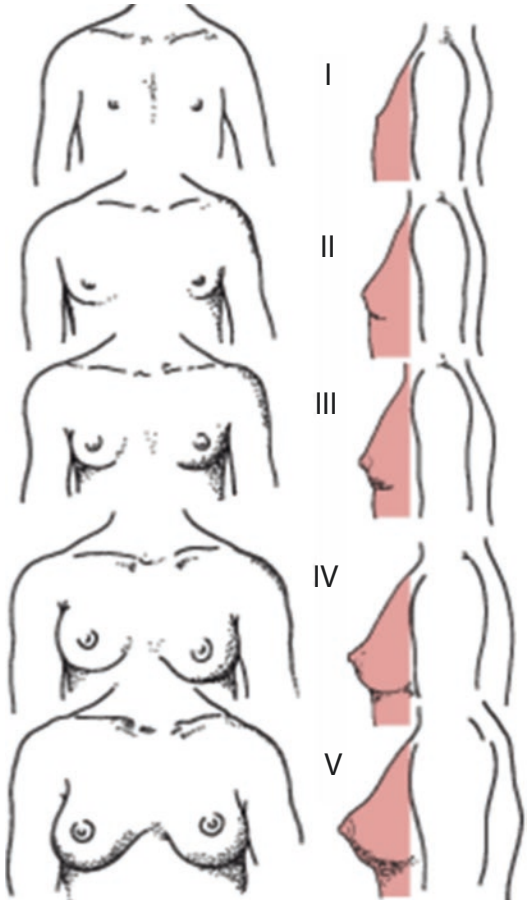

Fig. 38.4 The Tanner Stages I–V for breast development in girls. Used with permission from Marshall WA, Tanner JM: Variations in patterns of pubertal changes in girls. Arch Dis Child 1969;44:291–303

Menstruation occurs throughout a woman's reproductive life in the absence of pregnancy. Menopause is the permanent cessation of menstruation.

The average duration of bleeding is around 5 (normal range 3–7) days. The average blood loss per cycle is around 30 mL (normal range 15–80 mL) and is usually maximal on the second day. Menstrual blood does not usually clot (unless bleeding is very heavy), probably because of fibrinolysin and other factors that inhibit clotting (Dockeray et al. 1987). Menorrhagia is the term used to describe heavy blood loss which can be because of a number of different reasons, e.g. uterine fibroids, clotting disorders.

The median menstrual cycle length is 28 days (usual range 21–35 days in adult women; 21–45 in adolescents). In general, menstrual cycles are longer and most variable in the years immediately after menarche and immediately before menopause, when ovulation is less regular. Irregular periods are more likely to be anovulatory. Based on consensus the menstrual cycle begins and ends with the first day of menstruation (day 1).

As depicted in Fig. 38.5, oestrogen levels are low in childhood and start rising during prepuberty, reaching a critical level at puberty when the development of secondary sexual characteristics begins. The peak level induces the onset of menarche and remains at a similar level with

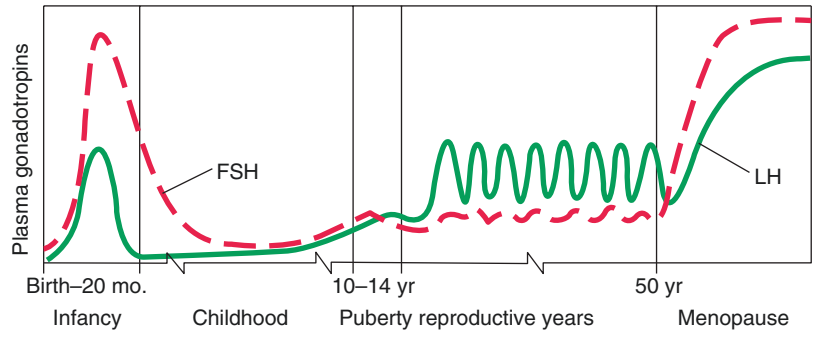

Fig. 38.5 LH and FSH levels throughout a female's life [Hall JE (2017) Disorders of the female reproductive system, chapter 13. In: Jameson JL (Eds) Harrison's Endocrinology, 4th Edition, McGraw Hill Education, New York, pages 192–201]

cyclical fluctuations during the woman's reproductive years, in synch with ovulation. Ovulation is irregular in the first few years following menarche and the few years prior to menopause (climacteric). After the menopause, the levels decline rapidly due to ovarian failure and lack of further production. The hormonal changes of the menstrual cycle cause ovulation and induce changes in the endometrium that prepare it for implantation.

38.4.1 Menstruation

The menstrual cycle is generally 28 days and includes the following phases: menstruation, proliferative phase, follicular phase and luteal phase.

Days 1–4 of the cycle is menstruation:

At the start of the menstrual cycle, the endometrium is lost and its hormonal support is withdrawn. Myometrial contraction, which can be painful, is accompanied by vasoconstriction to reduce blood loss.

38.4.2 The Proliferative Phase

Days 5–13 of the cycle are the proliferative phase:

The proliferative phase of the menstrual cycle can be sub-divided into two ovarian stages: follicular (pre-ovulatory) and luteal (post-ovulatory) phases.

The dominant follicle develops through a three-stage process: (1) Recruitment, (2) Selection, and (3) Dominance. Recruitment takes place during days 1–4 of the menstrual cycle, when FSH leads to recruitment of several follicles from the available cohort of non-proliferating follicles. Between days 5–7 of the cycle, a single follicle is selected amongst the recruited follicles, for ovulation and the remaining follicles undergo atresia. By the 8th day of the cycle, one follicle becomes dominant and promotes its own growth, suppressing the maturation of the other ovarian follicles thus becoming the dominant matured follicle, which subsequently releases its ovum in the process of ovulation (Fig. 38.6).

38.4.2.1 The Follicular Phase

This phase is the most variable in terms of length. During the early follicular phase (the first half), the recruited follicles become larger.

The gonadotrope cells in the anterior pituitary contain little LH and FSH at this stage. Oestrogen and progesterone levels are also low. However, pulses of GnRH from the hypothalamus stimulate LH and FSH release by the anterior pituitary. Overall, FSH secretion increases slightly, stimulating growth of the recruited follicles, with slower subsequent rise in circulating LH levels (1–2 days after the peak in FSH). The recruited ovarian follicles are eventually able to produce oestradiol which in turn stimulates the synthesis of LH and FSH but also inhibits their secretion, via a negative feedback mechanism. This usually results in only one follicle maturing and one ovum being released into the fallopian tube.

During the late follicular phase (second half), the follicle selected for ovulation matures and accumulates granulosa cells, which secrete hormones.

The antrum of the follicle enlarges with follicular fluid, reaching a size of approximately 18–20 mm immediately before ovulation. The levels of the gonadotropins decrease, with FSH being markedly more affected than LH. From this point on, the levels of FSH and LH begin to diverge because oestradiol inhibits FSH secretion more than LH secretion, but also because the developing follicles produce inhibin, a hormone which inhibits FSH secretion (Fig. 38.1), but not LH secretion (Berga and Naftolin 2012). Furthermore, the half-life of LH is around 20–30 min, whereas that of FSH is much longer at 2–3 h. Levels of oestrogen, particularly oestradiol, rise exponentially.

As the oestradiol levels continue to rise and reach their maximum, a positive feedback effect on the hypothalamus and pituitary, causes LH levels to rise sharply and ovulation follows.

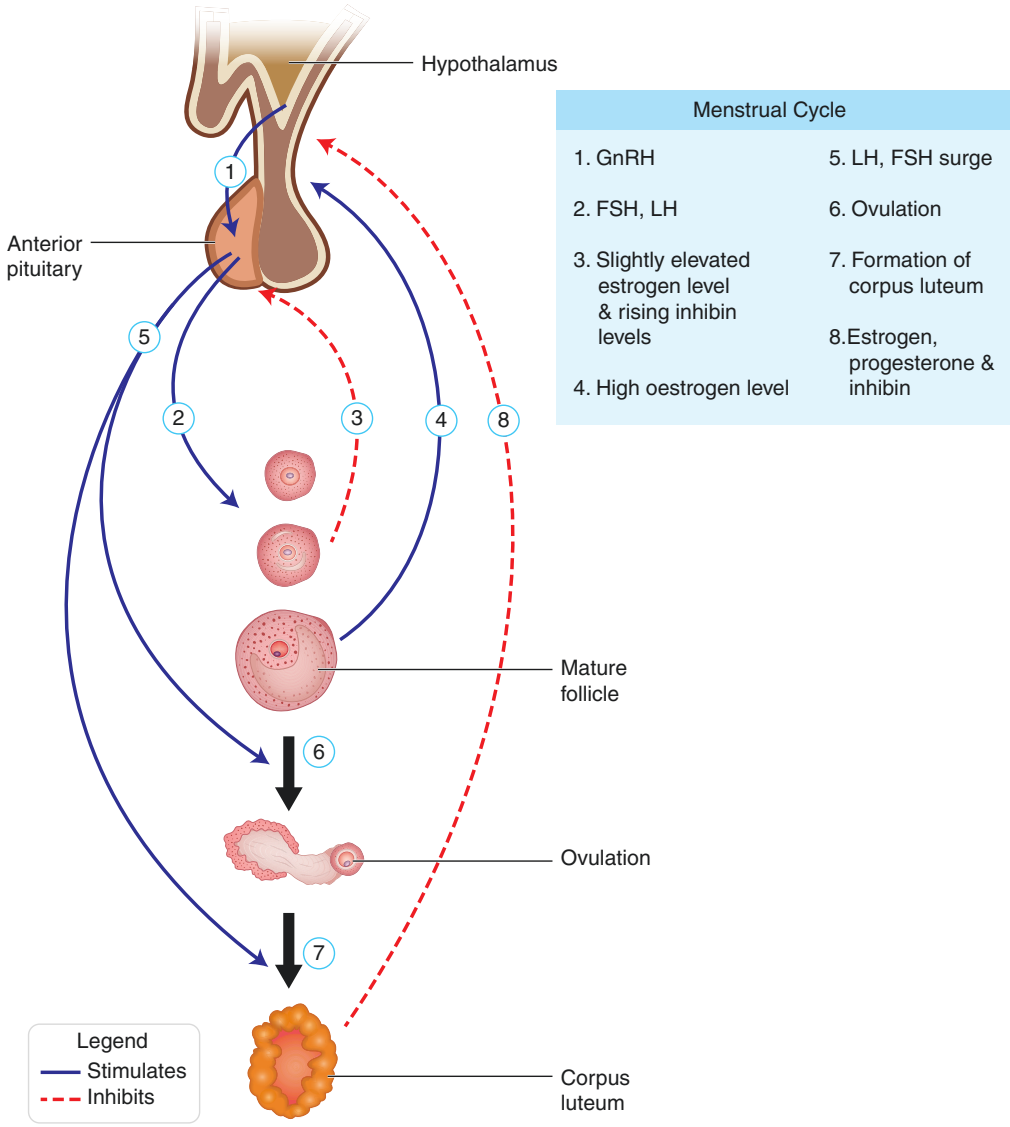

Fig. 38.6 Regulation of menstrual cycle and ovulation in the hypothalamic-pituitary-ovarian axis

Oestradiol levels usually peak as the ovulation begins. Progesterone levels also begin to increase. The LH stored in the pituitary is released in massive amounts in a process called the "LH surge", which occurs over 36–48 h. There is a smaller increase in FSH.

The LH surge occurs primarily because the high levels of oestradiol trigger LH secretion by the gonadotrope cells of the pituitary, via a positive feedback mechanism. The LH surge is also stimulated by GnRH and progesterone. The LH surge stimulates the release and activation of enzymes that initiate breakdown of the wall of the follicle and release of the now mature ovum within about 16–32 h. The LH surge also triggers completion of the first meiotic division of the oocyte within about 36 h. During the LH surge, the oestradiol levels decrease, but progesterone levels continue to rise (Fig. 38.6).

38.4.2.2 Luteal Phase

After releasing its ovum, the dominant follicle transforms into the corpus luteum. The length of this phase is the most consistent, averaging 14 days (range: 11–17 days). If pregnancy doesn't occur within these 14 days, the corpus luteum degenerates. A shortened luteal phase may indicate luteal phase deficiency (LPD) and a proposed diagnostic criterion for LPD is a shortened luteal phase of <9 days. However, a short luteal phase can occur in up to 5% of healthy fertile women which is often comparable to the luteal phase seen in the infertile population (Mesen and Young 2015).

The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg/day 6–8 days after ovulation. Progesterone stimulates development of the endometrium (the lining of the uterus), which is necessary for implantation of the zygote, should fertilisation occur and establishment of pregnancy. Progesterone is thermogenic, leading to an increase in the basal body temperature of about 0.5 °C.

During most of the luteal phase, the levels of circulating oestradiol, progesterone, and inhibin are high and negative feedback on the pituitary causes a reduction on the LH and FSH levels. Eggs can survive about 12–24 h after release (and sperm can live for 3–5 days). If pregnancy does not occur, the egg disintegrates and progesterone levels fall. About 12–16 days later, tissues from the lining of the uterus are expelled as menstrual bleeding and the cycle starts again. If pregnancy doesn't take place, oestradiol and progesterone levels fall late in the luteal phase and the corpus luteum degenerates, into the corpus albicans. If implantation does occur, the corpus luteum does not degenerate and remains functional in early pregnancy, with the support of human chorionic gonadotropin (hCG) that is produced by the developing embryo.

38.5 Pregnancy

During the luteal phase, progesterone stimulates the endometrium to change from proliferative to secretory form, which is very vascular and composed of spiral arteries. The glandular secretory endometrium secretes chemokines, growth factors, and cell adhesion molecules, all of which establish and maintain a favourable environment for implantation.

After ovulation and fertilization, the zygote (fertilised egg) remains in the ampulla of the fallopian tube for up to 3 days and undergoes a sequence of cell divisions, differentiation and eventually forms the morula (the group of cells from the dividing zygote). This process is independent of the hormones in the fallopian tube and uterus and can be performed in vitro during in vitro fertilisation (IVF). The morula then travels along the isthmus to the uterus, in a process that takes around 10 h and enters the uterus as an embryo. It continues to develop and 3–6 days after fertilisation, it becomes a blastocyst and floats in the endometrial cavity.

The blastocyst secretes several substances that improve the chances of implantation via enhanced maturation of the endometrium. These also render the endometrium more receptive to an imminent implantation. The success of implantation relies on the precise synchronisation between the developing blastocyst and the maturing endometrium. The blastocyst then becomes implanted into the thickened endometrium and implantation is complete (Fig. 38.7).

After implantation is initiated, the embryo actively secretes human chorionic gonadotropin (hCG), which stops the corpus luteum from disintegrating into the corpus albicans. This allows the corpus luteum to continue producing progesterone and therefore maintains the thickened endometrium for continued gestation. The main hormones produced by the corpus luteum are progesterone, 17 β-progesterone, oestradiol, and androstenedione. Low-density lipoprotein (LDL) cholesterol is the main precursor of these steroid hormones. The function of the corpus luteum naturally begins to decline between sixth and seventh week of gestation. The production of progesterone gradually shifts from the corpus luteum to the developing placenta, over a few days in a process called the "luteal-placental transition period", which occurs at approximately the seventh to ninth weeks of gestation.

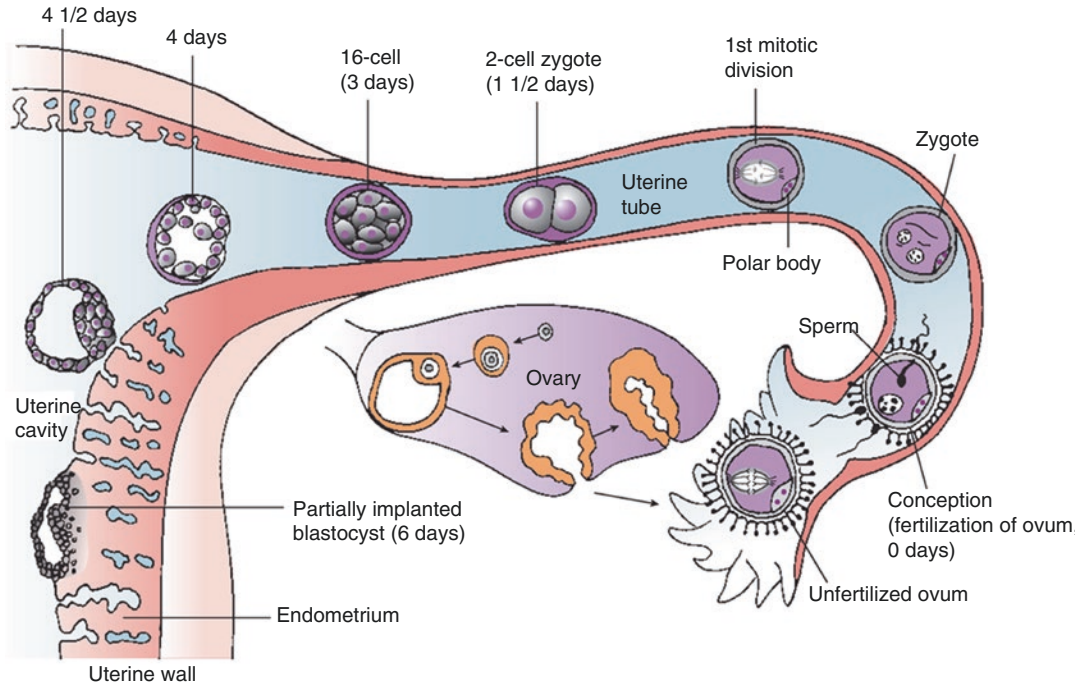

Fig. 38.7 The fertilisation and implantation stages

This process is vital for maintaining a viable pregnancy, as progesterone is the most important hormone as it can single-handedly maintain an early pregnancy that would be aborted if the corpus luteum was to be lost prematurely. Progesterone can be given as an injection to women pregnant through IVF from an egg donor to maintain the pregnancy, in the absence of a corpus luteum, during the first trimester until the secretion of progesterone is established by the placenta (Sauer et al. 1990). Similarly, in patients with corpus luteum dysfunction, exogenous progesterone is frequently administered until around the tenth week of gestation (Mesen and Young 2015; Sauer et al. 1990).

The outer blastomere cell layer of the blastocyst is known as the trophectoderm, and they can be identified at as little as 5 days following fertilisation. These cells eventually form the placenta. The main structural and functional units of the placenta are the chorionic villi, which increase in number during the first trimester of pregnancy. The villi provide a large surface area for absorption and nutrient and gaseous exchange between the mother and foetus. The maternal blood is delivered via the spiral arteries, circulates through the intervillous space, whilst the foetal blood moves in the core of the chorionic villi of the villous vessels. The foetal and maternal blood therefore never mix.

The trophoblasts are key cells within the chorionic villi, and they have the ability to multiply, invade, migrate, and differentiate through aggregation and fusion. By 10 days after fertilisation, the invading trophoblasts form two separate layers. The inner layer is called the cytotrophoblasts which are individual and rapidly dividing cells. The outer, thicker layer is known as the syncytiotrophoblasts which is a syncytial layer of multinucleate cells that line the placental villi of the foetal side of the intervillous space.

The syncytiotrophoblasts appear to be present in two distinct forms, each of which appears to produce either hypothalamic-like hormones: GnRH, CRH, and TRH or pituitary-like hormones: hCG, ACTH, and human chorionic thyrotropin (hCT). The Syncytiotrophoblasts are therefore the main site of hormone production in the placenta.

Due to their large surface area and the fact that they line the intervillous space, the hormones are directly released into the maternal blood stream, almost exclusively and at much higher concentrations compared to the foetal circulation.

The decidua (the endometrium during pregnancy) is a site of maternal hormone production, which maintains and protects the pregnancy from the mother's immune system. Cortisol secreted by the decidual endometrium in synergy with the foetal progesterone and hCG suppresses potential immunological rejection. The decidua also produces decidual prolactin which is a peptide hormone with identical chemical and biological properties to the pituitary prolactin and its production is induced by progesterone. It is released into the amniotic fluid and is not affected by administration of dopamine agonists (e.g. Bromocriptine and Dopamine) as its control is not dopamine dependent. It reduces the permeability of the amnion in the foetal to maternal direction and therefore regulates fluid and electrolyte movement through the foetal membranes. Pituitary prolactin is also secreted in the foetal circulation (by the foetal pituitary) and the maternal circulation (by the maternal pituitary) and these are both suppressed by maternal ingestion of Dopamine agonists.

Relaxin is a peptide hormone produced by the corpus luteum (in pregnant women only), the placenta, decidua, and chorion. Its main function in the mother appears to be with ripening (softening) the cervix, inhibiting uterine contractions and relaxing the pubic symphysis in preparation for labour. In the foetus, it binds to the foetal membranes, increases cytokine levels which in turn activate matrix metalloproteinases, and ultimately leads to a cascade of events that result in the rupture of membranes.

38.6 Menopause

This is a natural event that marks the end of spontaneous ovulation in a woman's life and therefore the ability to reproduce. The average age in the western world is 51 years (http://www.endotext.org). The classical symptoms of hot flashes, vaginal irritation, sleep disturbance, fatigue, and weight gain are most likely due to oestrogen deficiency. The symptoms are unique to each individual and vary markedly, with some women experiencing few or no symptoms and other women being majorly affected.

Menopausal transition (climacteric) usually starts in the late 40s and lasts around 5–7 years, with gradually reduced ovarian function. It is characterised by erratic ovarian oestradiol production and irregular length of menstrual cycle. FSH levels increase due to reduced inhibin produced by the granulosa cells. An FSH > 10 mIU/mL measured between 2–5 days of the cycle indicates ovarian aging (http://www.endotext.org). Oestradiol levels gradually become lower and lower and eventually secretion stops. The post-menopausal ovary no longer produces oestradiol but continues to produce androstenedione and testosterone at pre-menopausal levels. Oestrone produced via peripheral aromatisation of androstenedione is then the main circulating oestrogen.

While age at menopause ranges from 49–52 years, cigarette smokers can undergo menopause 1–2 years earlier compared to non-smokers (Gold et al. 2001).

Menopausal symptoms can be alleviated by the temporary replacement of oestrogen either orally or using patches. However, unopposed oestrogen action can lead to endometrial hypertrophy and ultimately increases the risk of endometrial cancer and therefore unless a woman has undergone a hysterectomy, she should be treated with combined oestrogen and progesterone preparations or have topical progesterone administration in the form of an intrauterine device, as well as the oestrogen replacement (please refer Chap. 41 in Part VI). The typical blood results of a post-menopausal woman is low oestrogen due to primary ovarian failure and high gonadotropins (LH and FSH), as the negative feedback of oestrogen has been removed. Initially, FSH and LH are high in the neonatal period, but by the age of 2, they drop, until a gradual increase during puberty. There is cyclical release during the fertile years and increase substantially in the post-menopausal period (Fig. 38.5), due to ovarian failure which results in low levels of oestrogen and therefore loss of negative feedback.

38.7 Conclusions

This chapter presented a summary of the anatomy and physiology of the female reproduction. It describes hormonal changes and how this influences the development of sexual characteristics and ovulation in a female throughout their lifetime.

References

Ameade EP, Garti HA. Age at menarche and factors that influence it: a study among Female University Students in Tamale, Northern Ghana. PLoS One. 2016;11(5):e0155310.

Apter D. Hormonal events during female puberty in relation to breast cancer risk. Eur J Cancer Prev. 1996;5:476–82.

Berga S, Naftolin F. Neuroendocrine control of ovulation. Gynecol Endocrinol. 2012;28(Suppl 1):9–13.

Choudhary S, Khichar S, Dabi D, Parakh M, Dara PK, Parakh P, Vyas S, Deopa B. Urban rural comparison of Anthropometry and Menarcheal Status of Adolescent School going girls of Jodhpur, Rajasthan, India. J Clin Diagn Res. 2016;10(10):SC08–12. Epub 2016 Oct 1.

Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. Eur J Obstet Gynecol Reprod Biol. 1987;24(4):309–18.

Flynn-Evans EE, Stevens RG, Tabandeh H, Schernhammer ES, Lockley SW. Effect of light perception on Menarche in Blind Women. Ophthalmic Epidemiol. 2009;16(4):243–8.

Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001;153(9):865–74.

Gueorguiev M, et al. Leptin and Puberty: a review. Pituitary. 2001;4(1–2):79–86.

Herman-Giddens ME, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997;99:505–12.

Hosokawa M, Imazeki S, Mizunuma H, Kubota T, Hayashi K. Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985. BMC Womens Health. 2012;12:19.

Knudston J, McLaughlin JE. Female reproductive endocrinology. 2018. https://www.msdmanuals.com/professional/gynecology-and-obstetrics/female-reproductive-endocrinology/female-reproductive-endocrinology. Accessed 16 June 2018.

Lee SE, Yang JY, Lee JH, Kim HW, Kim HS, Lee HJ, Oh JY, Sung YA. Relationship of age of menarche on anthropometric index and menstrual irregularity in late adolescent girls in Seoul. Ann Pediatr Endocrinol Metab. 2013;18(3):116–21.

Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child. 1969;44:291–303.

MedicineNET. Reproductive Health. 2018. https://www.medicinenet.com/reproductive_health/article.htm#menstruation_and_menopause. Accessed 16 June 2018.

Mesen TB, Young SL. Progesterone and the luteal phase. A requisite to reproduction. Obstet Gynecol Clin N Am. 2015;42(1):135–51.

Novello L, Speiser PW. Premature adrenarche. Pediatr Ann. 2018;47(1):e7–e11.

Rosenfield RL, et al. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.

Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. N Engl J Med. 1990;323:1157–60.

Seminara SB, et al. The GPR54 gene as regulator of puberty. N Engl J Med. 2003;349(17):1614–27.

Soliman A, De Sanctis V, Elalaily R. Nutrition and pubertal development. Indian J Endocrinol Metab. 2014;18(Suppl 1):S39–47.

Watanabe M, Fukuda A, Nabekura J. The role of GABA in the regulation of GnRH Neurons. Front Neurosci. 2014;8:387.

Zeydabadi Nejad S, Ramezani Tehrani F, Zadeh-Vakili A. The role of Kisspeptin in female reproduction. Int J Endocrinol Metab. 2017;15(3):e44337.