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FSH, Estrogens, Progesterone effects on female bodies during reproductive stages and their utilization in clinical practice and research

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Abstract

Sex hormones have been studied for more than a century. They affect almost all body systems and functions. FSH assists in converting androgens to estrogens; regulates bone mass, functioning of adipose tissue, energy metabolism, cholesterol synthesis; also, it has an impact on hepatocytes and tumor blood vessels. Estrogens are a family of hormones that consists of estrone, estradiol and estriol. The first two are biologically active estrogens in non-pregnant individuals, while the third one is produced in significant amounts during pregnancy. In non-pregnant females, estradiol circulates at higher concentrations, and it is more biologically active than estrone. Estrogens and progesterone spread their influence on the reproductive system, breasts, skin, adipose tissue, musculoskeletal, cardiovascular systems and brain functioning. Their levels fluctuate within lifespan, allowing clinicians and researchers to test them, monitor and predict different physiological events, conditions and disorders.

Radioimmunoassays, enzyme immunoassays, enzyme-linked immunosorbent assays, and mass spectrometry are commonly used methods for measuring parent hormones and their metabolites. Serum samples provide a more accurate picture, while saliva and urine are more convenient, as they are painless and can be easily collected by patients and analyzed at home. There is great utilization of hormonal testing in clinical practice, and at the same time a big potential in monitoring hormone levels for disease diagnosis and prognosis, pregnancy outcomes predictions in assisted reproduction, building and using algorithms for labor predictions, first signs of transitions to menopause that could be useful for fertility preservation.

Keywords: Estrogens, progesterone, FSH, reproductive hormones, estrogen metabolites, menstrual cycle, estrone glucuronide, pregnanediol glucuronide, aging, menopause transition

Introduction

The importance of female sex hormones is not under question, but what is the whole spectrum of their effects on bodies during different stages of the reproductive lifecycle. We're summarizing the evidence of their major role in different periods of the reproductive life cycle, and investigating whether enough of their potential is used for clinical decision-making and research, epidemiological studies, and what is still under attention.

FSH is a pituitary gonadotropin that was discovered in 1930 [1] during a research project that was led by Frederick Hisaw [2]. FSH is a heterodimeric molecule of the glycoprotein hormone family [3]. It consists of the α- and β-subunits. FSH induces folliculogenesis and estrogen production in females and regulates spermatogenesis in males [4]. In females, FSH stimulates the aromatase to convert androgens to estrogens. Besides its role in the reproductive system, FSH regulates bone mass, functioning of adipose tissue [5], energy metabolism, and cholesterol synthesis in both sexes; it also has an impact on hepatocytes and tumor blood vessels [6].

Estrogens were extracted in the 1920s by Edgar Allen

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and Edward Doisy [7]. They are a family of hormones that consist of estrone (E1), estradiol (E2) and estriol (E3), and are mainly secreted in females by the granulosa cells in the ovarian follicles, and also in adipose tissue. In males, they are produced by Leydig cells and the germ cells in testicles [8]. Adipose tissue becomes the main source of these hormones for postmenopausal females [9]. The first two (E1 and E2) are biologically active estrogens in non-pregnant individuals [10], the third one or E3 is produced in significant amounts during pregnancy. In non-pregnant females, E2 is more biologically active than estrone.

Progesterone is a steroid hormone that is released by luteinizing granulosa and by luteal cells in the adrenal cortex, as well as the ovaries. Progesterone was discovered by Alenn W.M. [11] because of its effect on embryo implantation and growth. The hormone was extracted from the corpus luteum in the 1920s [12]. It has been thought that progesterone is produced only during the luteal phase of a menstrual cycle, but in 1997, a study of females undergoing mid-follicular oophorectomy showed that after surgery serum progesterone concentrations decreased to an almost unmeasurable level [13]. This leads to conclusions that the ovaries can release progesterone even during the follicular phase of the cycle. During pregnancy, progesterone secretion goes to the placenta at the end of the first trimester [14].

Testing

A current approach for testing hormonal levels includes usage of different biological liquid samples, such as blood, urine and saliva, and is commonly performed using radioimmunoassays, enzyme immunoassays, enzyme-linked immunosorbent assays, and mass spectrometry methods [15] on laboratory equipment. In recent years, small portable devices have made testing possible at home, which is more convenient for patients. The advantage of serum testing is a more precise picture of hormone quantity, when samples are collected by trained staff, as self-collected blood samples add errors to the results that can be mitigated. At the same time, saliva and urine sample collection have the advantage of being a non-invasive painless approach.

A strong correlation between serum and urinary levels of FSH makes it possible for long monitoring of its levels with morning urine samples that reflect 24-hour concentration [16].

Conjugated and unconjugated urinary estrogen metabolites [15] could be measured in a single overnight sample, using the 4-spot rule, and with 24-h urinary collection. They are applicable for clinical purposes, as levels coincide with serum parent ones. Metabolism time should be taken into account when analyzing urine levels, as they reflect serum levels 12-24 hours prior to urine collection. High correlation between E2 serum levels and urinary metabolites was found with single metabolite detection, such as estrone-3-glucuronide, estriol-16-glucuronide, estradiol-17 beta-glucuronide, and sum of sulfate and glucuronide forms of E1 or E1 conjugates [16,17]. A stable isotope dilution liquid chromatography-tandem mass spectrometry (LC–MS2) method allows running the measurement of 15 estrogen metabolites and estrogens in serum and urine simultaneously, but also with a higher cost for the analysis [18].

Urinary pregnanediol glucuronide levels may be a more accurate representation of serum progesterone levels within 8 hour interval, as serum levels vary greatly during the luteal phase, reaching fivefold difference measured minute to minute, due to the pulsation of its production by the corpus luteum [15].

Methods

A PubMed, Google Scholar literature search was performed with selected keywords. Publications were limited by English language, but no publication date limit has been set, relevant manuscripts were derived from the reference list of selected manuscripts. Selected keywords: 'FSH', 'estrogens', 'oestrogens', 'estrogen metabolites', 'oestrogen metabolites', 'estradiol', 'oestradiol', 'progesterone', 'sex hormones', 'sex hormones levels', 'sex hormones impact on body', 'menarche', 'early puberty', 'menstrual cycle', 'estrogens effects during pregnancy', 'oestrogens effects during pregnancy', 'physiology of pregnancy', 'progesterone in pregnancy', 'estrogens effect on skin', 'oestrogens effect on skin', 'estrogens effects on musculoskeletone', 'oestrogens effect on musculoskeletone', 'sex hormones at menarche', 'FSH discovery', 'estrogens discovery', 'oestrogen discovery', 'progesterone discovery', 'transition to menopause', 'menopause and skin aging', 'musculoskeletone aging'. Only relevant manuscripts were extracted.

Main effects on female bodies

Ovaries are the main producers of estrogens and progesterone**.** Under the influence of FSH in the early follicular phase, antral follicles start development, growth, and with the help of luteinizing hormone, the dominant one ovulates. Then, in the place of the dominant follicle rupture, the corpus luteum is formed. It is a structure that produces progesterone in the second part of the ovarian cycle. Estrogen is believed to play a role in the structural and functional degradation of the corpus luteum.

Uterus: In the uterus, estrogens foster proliferation of endometrial cells and thicken endometrium in the follicular phase of the menstrual cycle. Rising progesterone levels in the early luteal phase stimulate secretory transformation of the endometrium [12,19].

Vagina: Estrogens, either endogenous or exogenous, support the proliferation of vaginal and vulva mucosa cells and prevent dryness and atrophy. For the females in transition to menopause, and after menopause, transvaginal administration of topical estrogens improves sexual life by reducing dryness and itching that causes discomfort.

Cervical mucus: There is also a visible effect of hormonal influence on cervical mucus changes. Cervical mucus is secreted

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to support lubrication and microbial clearance. It is composed of 92–95% of water, ions and 5–8% of solid matter [21]. The solid portion is mainly made up of mucin glycoproteins, proteoglycans, and lipids. Under the influence of rising estradiol levels before ovulation, the cervical mucus becomes transparent, copious and elastic and can be stretched for more than 10cm. The German term *spinnbarkeit* was used to describe this phenomena [22]. After ovulation, the cervical mucus once again thickens, reduces in quantity, becomes viscid and dense.

Breast: Estrogens are responsible for the development, parenchymal and stromal changes in breast tissue at puberty and pregnancy, secretion of breast milk after giving birth. Progesterone is a risk factor for breast cancer [23], because it stimulates cyclical proliferation of mammary stem cell pools or tumor initiating cells in the mature breast epithelium [23].

Under the influence of balanced levels of E2 and progesterone, mammary glands develop properly, so the main target for E2 is the ductal system, its growth, and for progesterone it is the development of lobules. In human beings, long periods of a luteal-phase defect (a condition when corpus luteum doesn't produce enough progesterone to transform endometrium to a level where it is hospitable for embryo implantation and development) [24] leading to an unopposed estrogen effect might be a promoter of carcinogenesis in the breast [25,26].

Skin: Estrogens mainly increase skin thickness, improve skin moisture, thereby preventing aging. Both sex hormones, estrogens and progesterone, stimulate proliferation of keratinocytes and suppress collagenolysis. Other effects of estrogens include: suppressing apoptosis, enhancing collagen synthesis, increasing levels of mucopolysaccharides and hyaluronic acid in the dermis and thus maintaining skin moisture. Progesterone increases sebum secretion [27,28].

Adipose tissue: Estrogens promote the accumulation of subcutaneous fat, and the loss of estrogen with menopause is associated with central fat deposition [29,30].

Bones: During puberty, estrogens aid in the development of long bones and the fusion of the epiphyseal growth plates. Estrogens protect bones by inactivating osteoclast activity, preventing fractures and osteoporosis.

Muscles: Estrogens improve muscle mass and strength, increase the collagen in connective tissue, and decrease stiffness in tendons and ligaments. High estrogen levels can reduce performance and make females more prone to ligament injury by increasing laxity and decreasing sinew stiffness. This association was shown in several studies where females had more injuries during the preovulatory peak of estrogens and the second peak in the luteal phase [31].

Cardiovascular: Estrogens have a protective effect on blood vessels and prevent coronary artery disease by decreasing low-density lipoproteins and total plasma cholesterol, and increasing high-density lipoproteins and triglyceride levels. Estrogens are also a hypotensive mediator, as they release endothelium-derived vasodilators and affect smooth muscle in vessels [32].

Gastrointestinal tract: In recent years, researchers have demonstrated that estrogens and their receptors serve a significant role in the gastrointestinal tract contributing to gastrointestinal diseases development, including esophageal, gastric and colon cancers, gastroesophageal reflux, peptic ulcers, inflammatory bowel disease and irritable bowel syndrome [33]. Progesterone slows down gastrointestinal motility, reduces the gallbladder's contractility, reduces the esophageal sphincter pressure, thus promoting gastroesophageal reflux, and protects from Helicobacter pylori [33].

Brain: Progesterone is believed to affect the function of the central nervous system, as a luteal phase of a menstrual cycle is associated with a variety of symptoms, such as irritability, mood swings, and/or depressed mood that start before and end within the first days of menstruation [12,34].

Limbic areas indirectly impact reproduction, neuroendocrine balance and additional functions, including emotional response and memory. The prefrontal regions ensure vertical modulation of limbic system function and are involved in emotional intelligence and decision-making [35,36]. In the study of female subjects that used magnetic imaging, it was shown that the orbitofrontal cortex response to emotional linguistic stimuli differed according to changing menstrual cycle phases. Thus in the late luteal phase, anterior-medial orbitofrontal cortex reaction to negative stimuli increased in comparison with the follicular phase when it dropped [35].

Menstrual cycle disorders, such as premenstrual syndrome, have been described and linked to changes in the hippocampus and parahippocampal gyrus, as well as somatosensory and pain pathway areas [10]. These areas, in addition to the thalamus and anterior cingulate cortex, take part in mediation of physical symptoms, including headaches, fatigue, nausea, menstrual cramps, and hyperalgesia [10].

There is evidence that some brain structures can change their size during menstrual cycle phases, thus the hippocampus is larger in the follicular phase, when estrogen levels are increased [37]. Therefore, some functional changes are possible in regards to structural ones, but data is inconsistent on that matter [38-40].

Immune system: Estrogens are believed to strengthen humoral immunity and, also, are associated with such autoimmune conditions as rheumatoid arthritis and systemic lupus erythematosus [41].

Early puberty

Female newborns have high levels of FSH during the first 5 months after birth, then levels decline until puberty [42]. Low levels of circulating estrogens suppress GnRH production in the hypothalamus [43]. This suppressive mechanism also has a central regulation, whilst it's not determined yet the way it contributes to the repression of the gonadostat [44]. Gonadostat theory was proposed in 1955 by Geffery Harris, a neuroendocrinologist, who researched structure-

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function relationships between brain structures, such as the hypothalamus and pituitary gland, and suggested that during puberty response to the inhibitory feedback action of gonadal steroids decreases [45].

Menarche

When gonadotropin releasing hormone secretion becomes pulsatile, it allows the pituitary to release LH and FSH [46]. LH activates androstenedione production in ovarian theca cells, and FSH rolls out estradiol synthesis in follicular cells. Growing estradiol levels make breast tissue enlarge and push linear bone growth. After a year of constant rise in daily estradiol, menarche occurs [47].

Menarche is the first menstruation with a decreasing global trend for its onset [48]. The mean age of menarche for developed countries is 12.25 - 12.86 years [49,50]; menarche age after 15 is associated with decreased fertility [51]. The determinants of the onset are continuously being researched, and it is believed that socioeconomic status [52], genetics, general health, nutrition, sport are contributing factors [53,54].

Positive estradiol feedback on the axis is not established within the first 6 to 12 months after menarche, and ovulation rarely occurs accordingly [55]. Progesterone levels remain low, and uterine bleeding cyclicity varies until the mechanism of LH surge influenced by estradiol is fully established, and ovulation becomes regular.

Testing

Hormonal testing of FSH during this period is recommended for teens with delayed puberty (e.g. Turner syndrome), and for those who develop sexual characteristics too early. In research of 131 children, urinary levels of FSH greater than 20.51 IU/l had 94.7% sensitivity and 91.3 % specificity for the diagnosis of hypergonadotropic-hypogonadism cases [56] while older studies had mixed results on that matter [57,58].

Reproductive stage

Menstruation is a cyclical bleeding that is caused by the shedding of the uterine lining in response to changing hormone levels. There are several evolutionary theories that explain the appearance of this biological event [59]. One of the theories describes it as an effect that helped eliminate infectious agents that come into the female body with sperm during sex. Other theories are focused on mother-fetal evolution. Thus, endometrium started differentiating and growing when embryos became more and more invasive [59,60].

Negative and positive mechanisms of ovarian feedback are responsible for the cyclic processes that take place in female bodies. They are not stable and change from birth to the menopause [61]. Before sexual maturity, only the negative feedback mechanism is active, then both are in place through the reproductive years, with a cancellation after menopause (as ovarian reserve is diminished).

There are two parallel processes that take place during the menstrual cycle: the ovarian cycle and the uterine cycle. The ovarian cycle will be used as a reference next in the text, it is divided by ovulation into the follicular, and the luteal phases. The uterine cycle consists of three phases: desquamation, proliferation and secretory [62,63].

Menstrual cycle length is calculated as the number of days between the first day of menstruation to the start of the bleeding in the next cycle. The mean duration of an ovulatory menstrual cycle is 29.3 days, according to the analysis based on 600,000 cycles [64]. In clinical practice it was common to use a 28-day cycle as a reference, but several studies confirmed that it's present only in 13-16% of the population [64-66]. According to the International Federation of Gynecology and Obstetrics (FIGO), normal menstrual cycle length is within a range of 24-38 days, with age-dependent cycle variability of 7-9 days, which can be applied to clinical practice as plus/minus 4 days [67]. The blood loss during menstruation varies from 5 mL to 80 mL, when it exceeds 80 mL, it is considered heavy [68].

The luteal phase duration is 7-17 days, with a mean of 12.4 days, and the follicular phase can vary from 10 to 30 days, with a mean length of 16.9 days [64].

FSH levels are elevated on days 2-4 of a menstrual cycle, this period is called 'FSH window', when selection of follicles takes place. Then levels return to the baseline, and surge again in 0.5 day before ovulation [69]. The median serum FSH levels on day 3 of a menstrual cycle are 6.1 IU/l (25th–75th range: 4.8–8.4 IU/l), with an increase of 0.11 IU for every year of age [70].

Estradiol levels are low in the early follicular phase, then they rise during the middle of the follicular phase and decline after ovulation. Ovulation occurs approximately a day after the LH peak, and 0.5 day on average after E2 peak (5th – 95th centile: – 2.5 – + 9.5 days) measured in urinary samples with detection of estrone-3-glucuronide, and 0.5 day after FSH peak (5th – 95th centile: – 2.5 – + 0.5 days), measured in urinary samples [69].

As it was shown in research, E2 is paramount for the endogenous LH surge, with a 200 pg/ml verge [61,71-73]. The second rise happens in the middle of the luteal phase, and levels decrease again closer to the menstruation. The median serum E2 concentration on day 3 of a menstrual cycle is 61 pg/ml (25th–75th range: 38–96 pg/ml) [70].

Progesterone induces a rise of FSH near ovulation, and decreased biologic effect of estradiol on the endometrium in the luteal phase. Steroid hormone levels begin to fall in the late luteal phase due to the degradation of corpus luteum, if pregnancy hasn't happened. Declining levels of progesterone in the late luteal phase trigger wriggling and constriction of the spiral arterioles, which results in decreased blood flow to the superficial endometrial layers and blood deficiency [14].

Testing

As hormonal levels fluctuate during the menstrual cycle, the

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attitude towards the frequency and intervals for measurements differs. Recent evidence shows individual variability in addition to intercycle variability, which makes the goal for accurate estimation of medium values even more challenging [74].

The current intention for hormonal monitoring is ovulation prediction (estrone-3-glucuronide and FSH), and confirmation (pregnanediol-3-glucuronide or PdG) for urine samples at-home, and in the laboratory testing serum levels of FSH, E2 and progesterone. Testing results help in diagnosis of polycystic ovarian syndrome, ovarian cysts, abnormal menstrual bleeding, ovarian tumors, hypogonadism, hypothyroidism, liver cirrhosis and other conditions.

FSH testing is used in diagnosis of premature ovarian insufficiency, ovarian cancer, pituitary adenomas; in couples with confirmed infertility in preparation for assisted cycles for decision making on ovarian reserve status, and prediction of pregnancy outcome; in cases of irregular menstrual cycles with variability greater than +/- 4 days; and in amenorrhea cases (Stress-Induced Hypogonadotropic Hypogonadism, Kallmann Syndrome) [75].

Pregnancy

Major changes happening in the body during pregnancy are caused by hormonal and anatomical changes due to a growing fetus. Progesterone and estrogens are key contributors to these changes, starting from fertilization to delivery, and facilitating the recovery process and lactation.

Ovaries: HCG production is initiated after implantation, allowing the corpus luteum to maintain production of progesterone, thus supporting pregnancy progression. Corpus luteum is the main source of progesterone up to ten weeks of pregnancy, then placenta takes this function, and corpus luteum degenerates. It happens around week 12 of pregnancy [76-78].

Uterus: Progesterone suppresses an estrogen-induced proliferative effect on endometrial lining, and activates genes responsible for the preparation of the endometrium for embryo implantation and trophoblast invasion [12,79]. Estrogens are mainly accountable for the uterine growth that starts from 70 g and reaches 1100 g by the end of the third trimester. The uterus returns to its pre-pregnancy size 23-24 days after delivery [80-82].

Vagina: Mucosa thickens, papillae enlarge, which leads to prominent vaginal rugae during pregnancy. Improved vascularity gives the vagina a bluish tone, and leads to an increased amount of whitish discharge [83,84]. Near the second trimester, the vaginal microbiome loses diversity and substantial amounts of Lactobacillus, which makes pregnant females prone to developing topical infections [85].

Breast: Breasts prepare for lactation during pregnancy and undergo several changes, thus they become larger, veins more prominent, areolas darker and larger, nipples more sensitive [84]. In animal studies it was shown that increased levels of progesterone and estrogens during pregnancy have a protective effect on the breast in relation to breast cancer, and in human studies E3 showed a protective effect [86-88].

Skin: Under the influence of elevated estrogen levels, it's typical for females to develop hyperpigmentation on the face, nipples, umbilicus, abdominal line, which is called linea nigra, and perineum. Also, some may have angiomas and palmar erythema [84]. Physical stretching of the skin, hormonal changes and genetics can destabilize the dermal connective tissue, and result in the appearance of stretch marks, and also trigger keloids emerging, as well as neuro- and dermatofibromas, leiomyomas, and cellulite [84].

Adipose tissue: Fat accumulation and storage rises in early pregnancy, which could be mainly caused by reduced postprandial lipid oxidation (pregnant women in comparison with non-pregnant). Also, the adipose tissue is mainly accumulated in preperitoneal rather than subcutaneous layers [89].

Cardiovascular: During pregnancy, blood volume increases, which ultimately leads to a gain in cardiac output, reaching a 60% rise in the third trimester. Systemic vascular resistance decreases under the influence of rising progesterone, which relaxes smooth muscles, resulting in falling arterial blood pressure [80,90].

Gastrointestinal: Nausea is very common and affects over 70% of pregnancies starting early on and usually resolves by week 14, sometimes persisting beyond week 20. The severe form of nausea and vomiting is called hyperemesis gravidarum, which is suspected if there is weight loss greater than or equal to 5% of pre-pregnancy weight, dehydration, electrolyte changes in urinary and blood tests. It's not established yet whether elevated levels of estrogen or progesterone, or possibly human chorionic gonadotropin, or even combined lead to nausea and vomiting during pregnancy [80].

Other hormonal effects include stomach reflux and constipation due to elevated levels of progesterone. Progesterone relaxes smooth muscle, which leads to prolonged gastric emptying time. If a person already has a decreased tone of the gastroesophageal sphincter it often results in reflux, as well as decreased motility in the large bowel, resulting in increased water absorption and constipation [80,91].

Brain: There is a U-shaped trajectory of the gray matter volume during pregnancy and postpartum: it decreases during pregnancy and then increases after delivery [92]. Gray matter volume changes of pregnancy can predict postpartum maternal attachment. In the prospective study, researchers measured brain changes in nulliparous and primiparous females during pregnancy and 2 years after giving birth using fMRI and attachment scale tasks. They used multivariate pattern classification analysis, which correctly classified females as having undergone pregnancy or not. Also, they analyzed brain changes in relation to three dimensions of the Maternal Postnatal attachment scale and suggested that these changes have an adaptive serving the transition into motherhood [93].

Subsequent longitudinal study of 47 females, which was a follow-up analysis of the previously described research,

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showed that brain changes caused by pregnancy are detectable even 6 years after delivery; at this period, the brain of a mother was still different from that of a nulliparous female [92]. Based solely on gray matter volume changes, researchers were able to classify females as having undergone pregnancy or not with 91.67% of total accuracy. Such brain changes may be related to the bond between mother and child after childbirth and could be long-lasting [92].

Bones: Pregnancy causes major changes in the skeleton, thus the center of gravity shifts, resulting in a notable lordosis of the lower back, neck flexion and shoulder depression. Also, joints become sluggish in the anterior and longitudinal ligaments of the lumbar spine; sacroiliac joints and pubic symphysis widen and increase mobility [91]. Scientific opinions and study results on maternal bone loss are controversial. Bone remodeling is low in the first trimester, increasing with fetal calcium requirements. Deposited skeletone calcium is the main source of this element in the third trimester [91].

Muscles: For up to 34% of pregnant females, restless leg syndrome is a known disorder. Current understanding of its origin lies between high estrogen levels, family history, Vitamin D, Calcium, Iron and folate deficiency [94,95].

Immune system: Pregnancy is a unique condition when the mother's immune system tolerates the fetus and is still responsive to other external pathogens. A more recent view on that subject is that immunological reactions during pregnancy result from the combination of reactions between the mother's and the fetal-placental immune systems [96]. Estriol, as well as estradiol, is likely one of the factors that contribute to enhanced humoral immunity during pregnancy, via stimulation of antibody production against innocuous antigens [96-99].

FSH

Starting from the first weeks of pregnancy, FSH levels decrease, from a median of 1.7 mIU/mL 6–10 days after ovulation to 0.1 mIU/mL in 26–30 days [100]. From the 5th week FSH response is almost inhibited. Approximately 20 days after delivery, FSH levels return to the follicular phase normal range [101,102].

Estrogens

Estriol (E3) is not present in non-pregnant females and is produced mainly by placenta making up almost 90% of estrogens during pregnancy. Estriol, similar to estradiol, induces immune response against innocuous antigens, and contributes to enhanced humoral immunity.

Estradiol production continues during pregnancy, its levels rise, peaking in the third trimester. Mean serum estradiol concentrations in their first trimester are in a range of 0.31–3.00 ng/mL, and 2.17–13.85 ng/mL in the third trimester [103].

Progesterone

Placenta is the main source of progesterone starting from the 10th week of pregnancy with ranging concentrations in serum from about 55 to 440 nmol/L [103,104]. After the 5th week of pregnancy, progesterone levels decline from 75.0 nmol/L, reaching 63.4 nmol/L at week 7, and then growing up to the third trimester [105].

Progesterone is essential for the conception, implantation and the maintenance of pregnancy; its administration delays delivery later in pregnancy, especially in pregnant females with short uterine cervixes [12,106].

Progesterone levels, as well as estrogen levels, rise during pregnancy, reaching their maximum in the third trimester and returning to their baseline after labor [107].

Testing

Serum level of estriol is used in maternal triple and quadruple screening tests. Typically they are done in the second trimester between 15 and 20 weeks of pregnancy to identify women who have higher chances of developing a fetus with a genetic condition (e.g. Down syndrome, neural tube defects) [108].

Assisted reproduction

FSH: Due to its role in follicle genesis, FSH is used in assisted reproductive technologies for ovarian reserve testing for better prediction of oocyte yield, and IVF cycle outcome [109]. This testing is based on the idea that females are born with a limited number of follicles that decreases during the lifespan: follicles are developed at 20 weeks, at birth female newborns have 1-2 million and the number declines, with a major reduction after 38 years, when it reaches approximately 24 thousand follicles [110].

According to the American Society of Reproductive Medicine (ASRM), FSH metabolites test is a sensitive and reliable marker of ovarian reserve, however should not be used outside of IVF cycles, as it doesn't predict the reproductive potential of females with unproven fertility [111].

FSH levels on the third day of the menstrual cycle are commonly used to help determine ovarian reserve, stimulation regimen and potential pregnancy outcome in infertile patients during preparation for IVF. In the retrospective study of 1298 infertile females it was suggested that the threshold for day-3 FSH was 12.7 mIU/mL. There was a negative association between FSH levels and delivery rates: delivery rates decreased significantly with increasing basal FSH ($p<.0001$) and absence of live births in females with an FSH > 28.1 or age > 45 [12,112,113].

Progesterone is vital for implantation and pregnancy maintenance in natural and assisted pregnancies. In a prospective cohort study of 127 participants, low serum progesterone levels during the luteal phase were associated with poorer pregnancy outcomes in assisted cycles. However, cause-effect remained unclear for researchers and could be investigated in another study, as after the same dose of progesterone, its serum levels differed among females, which could be a consequence of pregnancy outcome, or a cause on the contrary [114].

Pregnancy loss

Miscarriage occurs in 15% ~ 25% of clinical pregnancies

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[115-117], among which about 5% of couples experience recurrent pregnancy loss [118]. Sporadic mutations are the cause for more than 50% of pregnancy loss cases [119-121]. Measurement of progesterone, β-HCG and E2 levels during the first trimester may help in clinical diagnosis of unviable and ectopic pregnancies. A single serum progesterone assay can help differentiate viable and non-viable pregnancies, including ectopic pregnancy, but it is insufficient for a definite diagnosis [122,123]. Currently, there is heterogeneity in the approach to measurement of these hormones and cut-off values usage, which requires systematization [124-126]. In addition, FSH levels with a peak in a range of 9-14 days after LH surge could be used for prediction of pregnancy, and early prediction of pregnancy loss in epidemiological studies [127].

Labor

Estrogens and progesterone are important for labor initiation, impacting cervical effacement, and contraction onset. There are attempts to make labor more predictable than it currently is, therefore, Alonso et al presented machine learning algorithms for the prediction of whether spontaneous labor will occur from week 37 onwards, using hormonal levels of estrone sulfate, estriol, progesterone and cortisol [128]. These hormones were analyzed in saliva samples collected from 106 pregnant women since week 34. Estrogen and progesterone weren't directly related to the onset of labor, and the reason for that could be in their receptor interaction, which leaves myometrium intact. Myometrium becomes more susceptible to the hormones closer to delivery after progesterone withdrawal [128,129].

Postpartum period

High prolactin levels in the postpartum period suppress gonadotropin-releasing hormone secretion and thereby estrogens and progesterone, which results in anovulation during the first months of active lactation [130]. Progesterone and its receptor B enhance epithelial cell proliferation and differentiation. As a result, mammary glands ducts lengthen, and a vast network of branching develops. At the same time, progesterone inhibits lactogenesis during pregnancy, that's why withdrawal during the postpartum period is required to initiate lactation [12]. If progesterone levels don't decrease, lactation may not occur. Estradiol serum mean concentrations 1 year after giving birth are < 0.06 ng/mL (< 220 pmol/L) progesterone mean is 0.86 ng/mL [103].

Transition to menopause

Menopause is a physiological process in which the number of ovarian primary follicles decreases, estrogens and progesterone levels decline. It leads to anovulation, and finally results in termination of menstruation. During the transition period, the progesterone level declines more quickly than estrogens; both hormones reach their minimum after menopause (E2 and progesterone), while FSH levels go uninhibited and remain high [131].

FSH: During perimenopause, FSH levels start to rise seven years before final menstruation, and reach 47.6 mIU/mL two years before final menstruation, then after one year from final menstruation, levels peak at 54 mIU/mL, and downshift to 51 mIU/mL, remaining stable afterwards [132].

Estradiol: Estradiol levels decrease dramatically two years before the last menstruation. This decline continues up to two years after menopause, and reaches 21 pg/mL, and then remains stable, with a second major decline six years after menopause, reaching 18.8 pg/mL [133].

Progesterone: Progesterone levels also decrease in perimenopause, and reach approximately 48 ug/mg, measured in the Study of Women's Health Across the Nation (SWAN) using detection of PdG in urine samples [134].

Testing

Hormonal testing in transition to menopause and after menopause is recommended for decision-making on HRT prescription, for differential diagnosis of ovarian cysts and tumors, hypothyroidism, pituitary disorders, and deciding on breast cancer treatment prescription.

A study on premenopausal and postmenopausal females showed greater within-subject variability of FSH levels before menopause, and after menopause between-subject variability [135]. Researchers suggest that for adequate testing in premenopausal females, single testing is not sufficient, while for postmenopausal females, single testing is enough to understand average serum FSH levels.

Post menopause changes

After menopause, the ovaries do not produce estrogens, only testosterone. It does not contribute to the negative feedback system, resulting in high FSH levels, and low estradiol and progesterone levels, which also affects the positive feedback mechanism. The hypothalamic-pituitary system still can respond to exogenous administration of estrogens, and ovulation is absent, due to the ovarian insufficiency.

Ovaries: After menopause, ovaries undergo major structural changes, which affect both the cortex and medulla. The cortex loses follicles, becomes thinner and less noticeable. Furthermore, there are invaginations of the surface epithelium. The medulla undergoes the hyalinization of vessel walls, develops stromal fibrosis and scars.

Uterus: Uterine lining shrinks [136] with declining E2 levels after menopause, prevalence of fibro and leiomyomas decreases as well [137].

Vagina: Vaginal mucosa becomes thinner and drier due to decreased estrogens. It leads to reduced elasticity, mucosa frailness, and raised sensitivity to injuries.

Adipose tissue: Visceral fat accumulation increases. Adipocyte hypertrophy, inflammation, hypoxia and fibrosis in subcutaneous adipose tissue are common for postmenopausal females [138,139].

Skin: Estrogen deficiency adversely affects many physiological functions, including skin aging signs, such as atrophy, wrinkles, dehydration, and poor wound healing. Subcutaneous vascular circulation also changes, thus capillary blood flow decreases, and there is frequent vasodilatation in the dermal papillae that causes flushing [**140**,**141**].

Bones: Estrogen insufficiency disrupts osteoclastic and osteoblastic balance by increasing osteoclastic activity. This results in higher bone resorption and overall loss [**5**,**142**].

Cardiovascular: postmenopausal females are more likely to have cardiovascular disease, as estrogen is believed to positively affect artery wall elasticity. After menopause, estrogen deficiency causes vasoconstriction, and an increase in low-density lipoproteins.

Brain: Estrogens decrease in transition to menopause is linked to Alzheimer's disease [**143**]. The administration of exogenous progesterone showed improvement in verbal working memory in comparison with the placebo and may have a positive impact on cognitive function [**144**].

Testing

A lot of attempts were made to evaluate endogenous estrogen exposure and breast cancer risk in postmenopausal females. Increased 2-hydroxylation of parent estrogens was linked to breast cancer risk mitigation in several prospective studies that utilized LC-MS/MS assays to detect 15 estrogen metabolites and estrogens in serum and urine. The method showed high sensitivity, reproducibility and accuracy and has a great potential to be included in clinical practice for cancer prevention programs [**145**].

Current challenges

In all studies, either epidemiological or clinical, and for clinical decision-making, reliability of laboratory results is essential. While there is great progress in understanding what the challenges are, it's important not to underestimate certain aspects.

One of the challenges that should be taken into consideration for the longitudinal epidemiological studies and clinical research is inter-laboratory variability of the results of FSH serum samples that are stored for more than 11 months [**146**]. This variability is mainly caused by the difference in storage conditions. Also, urine samples for FSH testing have different activity periods depending on whether they are preserved or not [**147**].

Plasma and urinary gonadotropins correlation, as well as serum estrogens and progesterone correlation with their urine metabolites, is the next aspect that should be considered in evaluation of the results. As for the estradiol metabolites and progesterone metabolites measurement, liquid samples and dried urine assays showed a good alternative for serum evaluation [**15**].

Menstrual cycle phase and day for measurement, testing intervals, sample collection approach, as well as methodology used for analysis also contribute to the data heterogeneity.

Conclusions

Hormonal levels of FSH, estrogens and progesterone change during the reproductive years, thus triggering physiological and pathological processes in the female body. There is great utilization of hormonal testing in clinical practice and, at the same time, a big potential in monitoring urine and serum levels for disease diagnosis and prognosis, pregnancy outcomes predictions, building and using algorithms for labor predictions, first signs of transitions to menopause that could be useful for fertility preservation.

List of Abbreviations

E1: Estrone
E2: Estradiol
E3: Estriol
FIGO: the International Federation of Gynecology and Obstetrics
fMRI: Functional magnetic resonance imaging
FSH: Follicle stimulating hormone
GnRH: Gonadotropin-releasing hormone
HCG: Human chorionic gonadotropin
HRT: Hormone replacement therapy
IVF: in vitro fertilization
LC-MS2: liquid chromatography-tandem mass spectrometry
LH: Luteinizing hormone
PdG: Pregnanediol-3-Glucuronide
SWAN: Study of Women's Health Across the Nation

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	AT	KM
Research concept and design	√	--
Collection and/or assembly of data	--	--
Data analysis and interpretation	--	--
Writing the article	√	--
Critical revision of the article	√	√
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