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Physiological endocrinology and causes of disorders of the menstrual cycle

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ABSTRACT

The menstrual cycle is the result of a complex interaction between the hormonal system and the body's organs, namely the hypothalamus, pituitary, ovaries and uterus. Regular menstrual cycle is an indicator of women's reproductive health, changes in the menstrual cycle can be associated with ovarian-thyroid dysfunction and pituitary axis. This article aimsto understand the role of endocrinology in the process of the menstrual cycle as well as review the currently available literature on the causes of disorders of the menstrual cycle.The method used is Systematic Literature Review using the Preferred Reporting Items for Systematic Reviews (PRISMA) flow by collecting articles, according to those obtained from the PubMed database, Wiley Online Library, Science Direct and Cochrane, with the keywords "Menstrual cycle, hormone disruption, gynecological disease , and endocrinology" from the results of the analysis, 6 articles were selected that met the criteria. The conclusion ismany factors influence the occurrence of disturbances in the menstrual cycle that can affect reproductive health, including diabetes, night shift work schedules, nutritional intake, smoking habits, as well as psychological stress and anxiety during the pandemic due to the Covid-19 disease and vaccine administration.

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INTRODUCTION

Normal reproductive function that occurs in women is a repeated cycle of follicular development, ovulation, and preparation of the endometrium for implantation if fertilization occurs in that cycle. This regularity of ovulatory cycle patterns can occur through the precise functional and temporal integration of stimulatory and inhibitory signals from the hypothalamus, pituitary, and ovary (Hall, 2019).

The menstrual cycle is a physiological condition where there is a change in sex hormone levels in the body, which changes the lining of the uterine wall, and ovulation occurs in the ovaries, which indicates the maturity of the reproductive organs (Le, Thomas, & Gurvich, 2020). The menstrual cycle is the result of an integrated and complex interaction between several hormones and body organs consisting of the hypothalamus, pituitary, ovaries, and uterus (Barbieri, 2014). The process begins with the pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus into the pituitary portal vein system which regulates the synthesis of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the anterior pituitary and their secretion into the circulation. FSH and LH stimulate follicular development, ovulation, and corpus luteum formation and the secretion of estradiol, progesterone, and inhibin from the ovaries (Hall, 2019).

Regular menstrual cycle is an indicator of women's reproductive health, changes in the menstrual cycle can be associated with ovarian-thyroid dysfunction and pituitary axis(Rostami Dovom et al., 2016). Women with irregular menstrual cycles 87% suffer from polycystic ovary syndrome (PCOS); PCOS women with menstrual cycles of more than 35 days or oligomenorrhea are the result of ovarian dysfunction and insulin resistance(Du & Li, 2013). Irregular menstrual cycles are one of the symptoms of PCOS, which can be associated with DM2 and cardiovascular disease (CVD) (Hadaegh et al., 2016).

The balance between estrogen and progesterone and their signaling mechanisms are regulated to maintain a normal menstrual cycle and to support pregnancy. Estrogen and progesterone imbalance can interfere with their complex regulatory mechanisms, resulting in estrogen dominance and progesterone resistance. Gynecological diseases are strongly associated with unregulated steroid hormones and can cause chronic pelvic pain, dysmenorrhea, dyspareunia, heavy bleeding, and infertility, substantially impacting a woman's quality of life (MacLean & Hayashi, 2022).

The purpose of this study is to understand the role of endocrinology in the process of the menstrual cycle and to learn what causes disturbances in the menstrual cycle based on a literature study approach so that it is hoped that it can add insight and knowledge and can be used as a reference in efforts to improve reproductive health.

RESEARCH METHOD

This article uses the Systematic literature review method, namely by reviewing the articles obtained by searching the electronic database, using the Preferred Reporting Items for Systematic Reviews (PRISMA) flow. In searching for data, journal searches came from the PubMed database system, Wiley Online Library, Science Direct and Cochrane, with the keywords "Menstrual cycle, hormone disruption, gynecological disease, and endocrinology". The inclusion criteria used were articles published by international journals with publication time from 2018 to 2023, with the type of research article free full text - open access or original article/research. From the initial search results found 108 articles. Then from this number it was re-selected and determined 6 articles that were considered according to the inclusion criteria.

RESULTS AND DISCUSSIONS

This literature review is compiled through a selection of articles that have been reviewed and refers to research objectives. The author searched for articles using four data bases, namely PubMed, Wiley Online Library, Science Direct and Cochrane, and managed to identify 108 articles, then carried out a selection of similarities with the results of 0 articles, then screened titles and abstracts to get 106 articles, then selected based on original research. 91 articles. Then selected based on suitability for the topic to be discussed and free full text, 6 relevant articles were obtained. The literature obtained was synthesized using the narrative method by grouping extracted data similar to the results measured to answer the research objectives.

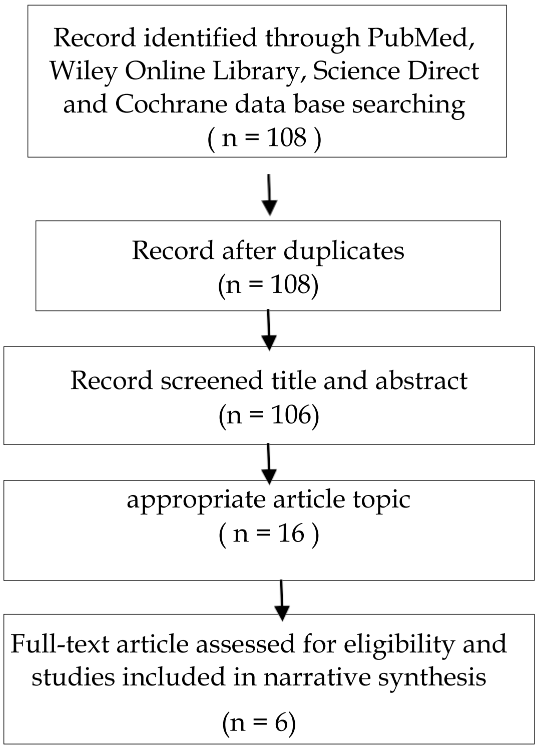

Figure 1. Article Search and Selection Flowchart

The results of research articles that match the inclusion criteria are combined in a table which includes the name and year of research, research title, research sample, statistical method, type of article, and research results, which are presented in table 1

Table 1. Summary of review results

No	Writer	Article Title	Research subject	Method	Article Type	Results
1	Kelsey, et al., 2018 (Kelsey et al., 2018)	Menstrual Dysfunction in Girls From the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study	Adolescent female patients who did not receive hormonal contraception and those who were at least 1 year after menarche.	Secondary analysis of Treatment Options for Type 2 Diabetes in Youth (TODAY) data	Original research	Of the 190 participants with an average age of 14 years, 21% experienced irregular menstruation. Menstrual dysfunction is common in girls with newly diagnosed type 2 diabetes and is associated with changes in sex steroids but not with changes in insulin sensitivity.
2	Stock, et al., 2019 (Stock et al., 2019)	Rotating night shift work and menopausal age	80,840 women from the Nurses' Health Study 2 (NHS2), with prospective follow-up from 1991 to 2013. Loss to follow-up from NHS2 is estimated to be <10%.	Cohort study	original article	During follow-up, 27 456 women (34%) reached natural menopause. Women who worked 20 months or more night shifts in the previous 2 years had an increased risk of early menopause (MV) - HR = 1.09, 95% CI: 1.02–1.16) compared with women

No	Writer	Article Title	Research subject	Method	Article Type	Results
						without night shift rotation work shift.
3	Stopa, et al., 2021 (Stopa et al., 2021)	Neonatal overfeeding reduces estradiol plasma levels and disrupts noradrenergic-kisspeptin-GnRH pathway and fertility in adult female rats	Female Wistar rats were obtained from mating 42 females with males from Central Bioterium Londrina State University (UEL)	prospective study	original article	this study demonstrates that neonatal overnutrition caused by reduced litter size promotes reproductive dysfunction in female rats not only at puberty, as previously reported, but also in adulthood, with lower plasma levels of estradiol, associated with impaired fertility and noradrenaline. - kisspeptin-GnRH pathway during positive feedback.
4	Florek, et al., 2022 (Florek et al., 2022)	Differences in sex hormone levels in the menstrual cycle due to tobacco smoking-myth or reality?	153 women of reproductive age, who received treatment at the Gynecological-Obstetric Clinical Hospital of the Poznan University of Medical Sciences. Divided into three groups: non-smokers, passive smokers, and smokers	Case control	Original research	Smoking can be an important factor in interfering with reproduction: 1. Increased levels of estradiol E2 are accompanied by a significant decrease in serum cotinine concentrations in tobacco smokers; 2. In smoking patients, serum LH levels significantly increases in the first days of the menstrual cycle; 3. Higher P levels (on days 14 and 21) are assumed to be result of longer menstrual cycles.
5	Madendag, et al., 2022 (Madendag, Madendag, & Ozdemir, 2022)	COVID-19 disease does not cause ovarian injury in women of reproductive age: an observational before-and-after COVID-19 study	A total of 132 young women aged 18–40 years were enrolled; they were tested for reproductive function in the early follicular phase, and the information was obtained from hospital data between January 2019 and June 2021. Serum FSH, LH, estradiol, ratio of FSH to LH and concentration of anti-Müllerian hormone (AMH) were measured for each patient before and after the COVID-19 disease.	observational study	Original research	In women with unexplained infertility, mean (and range) AMH serum concentrations were 2.01 ng/ml (1.09–3.78) and 1.74 ng/ml (0.88–3.41) in the pre-COVID-19 disease and post-COVID-19 disease groups, respectively. There was no statistically significant difference in serum AMH concentrations between before and after death (P=0.097). The ratios of serum FSH, LH, FSH/LH and estradiol concentrations of patients before COVID-19 illness were similar to those of the same patients after COVID-19 illness.
6	Wang, et al., 2022 (Wang et al., 2022)	A prospective study of the association between SARS-CoV-2 infection and COVID-19 vaccination with changes in usual	3,858 premenopausal women received biannual follow-up questionnaires between January 2011 and December 2021 and completed additional monthly and quarterly	Prospective study	Original research	Vaccinated women had a higher risk of increased cycle length than unvaccinated women (odds ratio, 1.48; 95% confidence interval, 1.00e2.19), after adjusting for sociodemographic and

No	Writer	Article Title	Research subject	Method	Article Type	Results
		menstrual cycle characteristics	surveys regarding the COVID-19 pandemic between April 2020 and November 2021.			behavioral factors. These associations were similar after accounting for pandemic-related stress. COVID-19 vaccination was only associated with a change to a longer cycle in the first 6 months after vaccination

Discussions

Research conducted by Kelsey, et al. (2018) aimed to characterize women with menstrual irregularities and the effects of glycemic medication on menstruation and sex steroids in the Treatment Options for Type 2 Diabetes in Youth (TODAY) study. Subjects studied were TODAY women who did not receive hormonal contraception and those who were at least 1 year postmenopausal were included. The results of this study showed that of the 190 participants with an average age of 14 years who met the requirements for sex steroid serum measurements, 21% experienced irregular menstruation. Those with irregular vs regular menstruation had higher body mass index (BMI) (P = 0.001), aspartate aminotransferase (AST) (P = 0.001), free androgen index (P = 0.0003), and total testosterone (P = 0, 01) and lower sex hormone binding globulin (SHBG) (P = 0.004) and estradiol (P = 0.01). So it was concluded that menstrual dysfunction often occurs in girls with newly diagnosed type 2 diabetes. . These irregular menstruation
was associated with higher testosterone and AST and lower estradiol concentrations but not with changes in insulin (Kelsey et al., 2018).

The Cohort Study by Stok, et al. (2019) performed on 80,840 women from the Nurses' Health Study 2 (NHS2), with prospective follow-up from 1991 to 2013. With follow-up loss from NHS2 estimated at <10%. During follow-up, 27 456 women (34%) reached natural menopause. Women who worked 20 months or more night shifts in the previous 2 years had an increased risk of early menopause (MV) - HR = 1.09, 95% CI: 1.02–1.16) compared with women without night shift rotation. This risk was stronger among women who were postmenopausal or under age 45 (MV-HR = 1.25, 95% CI: 1.08–1.46), than among those who continued at age >45 (MV -HR = 1.05, 95% CI: 0.99–1.13). Working 10 years or more of cumulative shifting night work was also associated with a higher risk of menopause among women who reached menopause under age 45. This study shows that premenopausal women who exceed the night shift work rotation threshold may be at risk of experiencing accelerated menopause (Stock et al., 2019).

Stopa, et al. (2020) conducted a study evaluating the effects of neonatal overfeeding on fertility and the noradrenaline-kisspeptin-gonadotrophin (GnRH) releasing hormone pathway in adult female rats. this study demonstrates that neonatal overnutrition caused by reduced litter size promotes reproductive dysfunction in female rats not only at puberty, as previously reported, but also in adulthood, with lower plasma levels of estradiol, associated with impaired fertility and noradrenaline. - kisspeptin-GnRH pathway during positive feedback (Stopa et al., 2021).

Based on Florek's research, et al. (2021), Smoking can be an important factor in interfering with reproduction. Where the results were obtained: 1. In tobacco smokers there was an increase in estradiol E2 levels accompanied by a significant decrease in serum cotinine concentration; 2. Serum LH levels are significantly increased in smoking patients in the first days of the menstrual cycle; 3. Higher Progesterone levels (on days 14 and 21) are thought to result from longer menstrual cycles. Active and passive smoking can be a cause of reproductive health problems (Florek et al., 2022).

Madendag, et al. (2022), conducted an observational study on 132 young women aged 18-40 years before and after suffering from COVID-19. By measuring serum FSH, LH, estradiol, the ratio of FSH to LH and the concentration of anti-Mullerian hormone (AMH). Concluded that ovarian reserve is not affected by the SARS-CoV-2 virus; however, changes in menstrual status may be related to extreme immune and inflammatory responses, or psychological stress and anxiety caused by COVID-19 disease. This change in menstrual status is also not permanent and heals within a few months after the COVID-19 illness (Madendag et al., 2022).

According to research by Wang, et al. (2022), 3,858 premenopausal women who were prospectively observed showed that vaccinated women had a higher risk of increased cycle length than unvaccinated women (odds ratio, 1.48; 95% confidence interval, 1.00e2.19), after adjusted for sociodemographic and behavioral factors. COVID-19 vaccination was only associated with a change to a longer cycle in the first 6 months after vaccination. COVID-19 vaccination may be associated with short-term changes in the usual duration of menstrual cycles, especially among women who had short, long, or irregular cycles prior to vaccination (Wang et al., 2022).

Characteristics of the Menstrual Cycle

The menstrual cycle starts from menstruation on the first day until the next menstrual period comes, and the length of the menstrual cycle is calculated from the start date of the previous menstruation until the start date of the next menstruation (Prayuni, Imandiri, & Adianti, 2019).
The length of one menstrual period varies in women of childbearing age between the ages of 20 to 45 years, where at this fertile age the cycle length is usually between 24-35 days (Le et al., 2020). Bleeding during menstruation is normal is 3 to 7 days. Menstrual bleeding that lasts less than 3 days is called hypomenorrhea. Menstrual bleeding that lasts more than 7 days is called hypermenorrhea. In one cycle, the normal amount of menstrual blood loss is 80 ml or less. Meanwhile, menstrual bleeding that exceeds 80 ml in one cycle is defined as menorrhagia which can result in a reduction in iron in the body and the risk of anemia (Barbieri, 2014).

The hypothalamus

The hypothalamus is a small area of nerve fibers and a nuclear body in the middle of the brain that serves many functions. The hypothalamus lies below the thalamus, which is bounded by the hypothalamic monro sulcus. The optic chiasma, which contains the preoptic nuclei involved in reproduction and feeding habits, surrounds the hypothalamus anteriorly. In the middle lies the tuber cinereum, called the rea tuberal. The middle region contains the mammillary, posterior hypothalamic, supramammillary, and tuberomammillary nuclei. At the bottom of the hypothalamic tube is the pituitary gland, which is connected to the hypothalamus through the hypothalamus-pituitary tract. The hypothalamus regulates hormone expenditure in the body based on releasing and inhibiting factors, namely releasing thyrotropin, releasing corticotropin, dopamine, somatostatin, and gonadotropins. These hormones are responsible for the processes of growth, body metabolism, homeostasis, and reproduction. As a reproductive function, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH) to stimulate the production of progesterone and estrogen in the gonads (Pop, Crivii, & Opincariu, 2018).

GnRH

GnRH (gonadotropin-releasing hormone) is secreted in the arcuate nucleus of the hypothalamus, which is a decapeptide structure. In the hypothalamus, two centers can be found, namely, in the ventromedial area of the arcuate nucleus called the tonic center, and in the preopticus area near the suprachiasmatic nucleus called the cyclic center, which has a different function. These two centers have a function, namely for the cyclic center to regulate LH production in the middle of the menstrual cycle and for the tonic center to regulate the daily basal needs of gonadotropin hormones. GnRH is released to the pituitary via the pituitary-hypothalamic tract, and in the anterior pituitary it binds to cell surface gonadotropin receptors (Suparman & Suparman, 2016).

GnRH neurons in the hypothalamus receive nerve signals from the brain and convert them into endocrine output, GnRH pulsatile release.The arcuate nucleus is a neuroendocrine transducer that can convert electrical signals into endocrine signals. GnRH is secreted into the pituitary portal circulation in a pulsed manner. The frequency and amplitude of GnRH pulses are influenced by several neuroendocrine modulators, namely kisspeptin, leptin, ovarian steroids, and peptides. These signals link between environment and reproductive status. The hypothalamus reviews various environmental cues including body composition and body mass, nutritional status, energy expenditure (exercise), stress, and emotional state which can determine the frequency and amplitude of GnRH pulses (Barbieri, 2014).

Kisspeptin

Kisspeptin is a very potent LH stimulator. The kisspeptin system is thought to play a major role in early puberty and is also involved in the negative feedback of estrogen in the median eminence. The response to kisspeptin is consistently strong in postmenopausal women and also during the menstrual cycle, namely in the late follicular, preovulatory, and luteal phases, but there are several cases of no LH response to kisspeptin (Clarke & Dhillo, 2016).

Kisspeptin stimulates GnRH release. Where the peptide derived from kisspeptin has a strong affinity for GnRH. Thus kisspeptin is thought to be an integrated part of the function for secreting GnRH and for the pubertal stage. So if there is a mutation in the kisspeptin gene it can result in hypogonadotropic hypogonadism, and have an impact on early puberty (Harter, Kavanagh, & Smith, 2018).

Leptin

Several studies explain the ability of leptin to modulate the nervous system which functions to control reproductive biology where the activity of the neural network has an effect on the release of GnRH, therefore leptin is also involved in regulating sex hormones (Zhang & Chua, 2018) (Al-Hussaniy, Alburghaif, & Naji, 2021). In addition, the hormones estrogen and progesterone affect the increase in leptin synthesis (Al-Hussaniy et al., 2021).

When the body is low in fat content, leptin levels also decrease causing the stimulus to secrete GnRH to decrease. And when the body's fat content reaches optimal levels, the release of GnRH will support the menstrual cycle and ovulation (Zhang & Chua, 2018).

Pituitary gland

The pituitary gland or pituitary gland is the main link between the brain and ovarian function. Pulsating release of GnRH stimulates the pituitary to secrete LH and FSH. The pituitary gland translates the tempo set by the hypothalamus into gonadotropin signals that control ovarian follicular activity and ovulation (Barbieri, 2014).

At maturity the pituitary gland is approximately 10 mm long, 10 to 15 mm wide, and about 5 mm high. In general the female gland is almost 20% heavier than the male gland mainly because of the relative difference in pars distalis size. The pituitary gland is located in the pituitary fossa, a fibro-osseous compartment near the center of the cranial base. This fossa is bounded laterally and superiorly by the reflection of the dura and elsewhere by the sella turcica, a notch in the body of the sphenoid bone. There, the glands have proximity to several important cranial nerves and vascular structures at the base of the skull (Amar & Weiss, 2003).

The anterior lobe has cells that secrete gonadotropins (LH and FSH), thyrotropin, growth hormone, corticotropin, or prolactin. Pituitary gonadotropins receive signals in the form of GnRH pulses from the hypothalamus. Then the pituitary responds to the signal by synthesizing and releasing FSH and LH that correspond to the GnRH signal (Barbieri, 2014).

Gonadotropins

In the pituitary gonadotropins, GnRH stimulates the formation and release of two gonadotropins, namely luteinizing hormone (LH) and follicle stimulating hormone (FSH), which function to regulate gametogenoidogenesis and gonads in both sexes. GnRH pulses have a very important role in the maintenance of gonadotropin gene expression and physiological patterns of gonadotropin secretion (Maggi et al., 2016). LH, FSH, and hCG bind to G-protein coupled receptors to stimulate target cells. The LH receptor binds LH and hCG. LH receptors are expressed in granulosa, theca cells, corpus luteal ovaries and testicular Leydig cells. FSH receptors are expressed in testicular Sertoli cells and ovarian granulosa cells (Barbieri, 2014)

The hypothalamic-pituitary unit increases GnRH, LH, and FSH secretion, thereby stimulating the growth of a cohort of small follicles. In a group of small growing follicles, one follicle achieves more rapid growth and secretes increased amounts of estradiol and inhibin A and B. This results in suppression of FSH and arrest of growth of all but the most dominant follicles. The increase in estradiol levels causes the LH surge which finally initiates ovulation. Within 12 hours of the LH surge, progesterone levels begin to rise and estradiol levels begin to fall due to follicular luteinization. During the luteal phase of the cycle, FSH levels are low, inhibiting the growth of new follicular cohorts, LH pulses are very slow, and progesterone levels peak in the middle luteal phase. If pregnancy does not occur (Barbieri, 2014).

Ovary

Embryonic development period

During embryogenesis, the primordial germ cells migrate from the yolk sac to the mesonephric ridge, where the ovary develops. Primitive germ cells, or oogonia, divide by mitosis, and when mitosis stops, they increase to millions at around 6 months of intrauterine development. From 8-13 weeks of gestation, all oogonia enter meiosis, all of which are converted into oocytes. This process is complete within the first 6 months of life. The oocyte remains suspended in meiotic prophase until stimulated to continue meiosis during the LH surge of each ovulatory cycle. The number of eggs continues to decline throughout life. During puberty, only 300,000 eggs remain and only a few hundred ovulate in a woman's lifetime (Barbieri, 2014).

Development of Follicles

About 1,000 primordial follicles begin the process of becoming primary follicles. Early in development, the granulosa cells surrounding the oocyte increase in size and produce estrogen as a result of initial FSH stimulation but later estrogen production becomes an autonomous process by the granulosa cells. The zona pellucida develops as well and becomes the outermost part of the oocyte and is in a protective sheath where sperm must penetrate to fertilize the egg after ovulation (Holes, Bass, & Lord, 2021).

Some of the primary follicles develop into secondary follicles, in which a layer of theca cells forms. Theca cells are stimulated by LH to synthesize androgens, which diffuse into the granulosa cells as estrogen precursors. The follicle then develops a fluid-filled cavity called the antrum. At this stage, it is referred to as antral, or Graafian, follicle. The follicular phase of the menstrual cycle occurs when antral follicles develop into preovulatory follicles in preparation for ovulation. The follicular phase begins on the first day of menstruation until day 14, namely ovulation of a 28 day cycle. FSH-dependent antral follicles compete with other developing follicles. The dominating follicle is called the "dominant follicle" and the others become atretic. The antral or “dominant” follicle secretes estrogen and inhibin, which provides negative feedback on FSH, thereby "turning off" the other antral follicles. The majority of follicles that begin the maturation process will atresia leaving one mature follicle for ovulation. If more than one follicle ovulates in one cycle, multiple pregnancies are not identical (Holesh et al., 2021).

Ovulation

The process of ovulation is on the 14th day of the 28 day menstrual cycle. Granulosa cells in the follicles increase estrogen production so that estrogen levels in the body increase. Estrogen transitions from the negative feedback modulator of GnRH to the positive feedback modulator in the hypothalamus, causing an increased frequency of GnRH secretion into the anterior pituitary, resulting in an increase in LH. With increased LH levels, intrafollicular proteolytic enzymes also increase, causing the ovarian wall to weaken so that mature follicles can pass through. The increase in LH also causes luteinization of theca and granulosa cells to form the Corpus Luteum, which functions to synthesize progesterone. The released follicle is then captured by the fimbriae of the fallopian tube. If fertilization does not occur, the oocyte remains in metaphase II of meiosis II (Reed, Carr, & Feingold, 2018).

Luteal phase

The luteal phase occurs on days 14 to 28 of the cycle. At first the corpus luteum is formed and pregnancy can occur or the corpus luteum is destroyed. FSH and LH stimulate the remaining mature follicles after ovulation to become the corpus luteum. The corpus luteum develops and secretes progesterone and estrogen, which prepare the endometrium for implantation. If fertilization does not occur, progesterone and estrogen levels decrease, and the corpus luteum becomes the corpus albicans. The decrease in hormone levels stimulates FSH to start preparing the follicles for the next cycle. If fertilization occurs, the human chorionic gonadotropin (hCG) produced by the early placenta maintains the corpus luteum and maintains progesterone levels until the placenta can produce optimal progesterone to support pregnancy (Reed et al., 2018).

Endometrium

Endometrial Endocrinology

The endometrium is very important in the reproduction and maintenance of our species. Where the endometrium has a function to prepare for implantation. In the endometrium implantation will occur if pregnancy occurs and to maintain it but if pregnancy does not occur then menstruation will occur (Critchley, Maybin, Armstrong, & Williams, 2020).

The endometrium undergoes morphological changes that occur under the influence of the sex steroid hormones, estrogen and progesterone. Estrogen and progesterone regulate endometrial receptivity. Endometrial receptivity is a complex process which is a requirement that must occur for successful embryo implantation to occur (Altmäe & Aghajanova, 2019).

Estradiol stimulates endometrial epithelial cell proliferation, glandular growth, and glandular vascularization. After ovulation, the endometrium responds to rapid increases in progesterone with changes in luminal cell secretion, further glandular development, decidualization of stromal cells, and development of spiral vessels. If no pregnancy occurs (Barbieri, 2014). During menstruation, more than three quarters of the endometrial lining is lost. Leaving a thin basalis where scarfree regeneration. Regeneration is influenced by estradiol which makes the endometrium grow from less than 2mm to 7mm at the end of the proliferative phase. If fertilization occurs, the level of progesterone increases and the endometrial stroma begins to differentiate. However, if fertilization does not occur, one week after ovulation, steroid levels reach a maximum and then decrease resulting in menstruation (Applin, 2018).

Proliferation Phase

After menstruation, the lining of the uterus gradually grows back under the stimulation of estrogen. The initial proliferative phase begins on day 4-7. Mid cycle proliferative phase 8-11 and late cycle day proliferative phase 11-14. During the early proliferative phase, the endometrium is less than 3 mm thick. The glands are short, narrow, tubular, and straight, lined with low columnar cells with rounded nuclei near their bases. There are multiple mitoses in the gland. The endoplasmic reticulum and Golgi apparatus are underdeveloped. During the intermediate proliferative phase, the gland is longer and has a slightly curved effect. The initial pseudo-layers of the nucleus appear in layers. There are many mitoses in the gland. During later proliferative stages, the gland is tortuous due to active growth. The luminal cells increase in height and become pseudostratified. There are many mitotic and pseudostratified nuclei. Stoma is dense and has many mitoses (Barbieri, 2014).

Secretory Phase

Ovulation marks the start of the secretory phase. The endometrium stimulated by estradiol undergoes differentiation under the influence of progesterone during the secretory phase. The first 7 days of the secretory phase are marked by the following sequential changes: appearance of basal vacuoles and persistence of mitosis in the glands and stroma (until 3 days after ovulation), increased indentation of the glands, prominent subnuclear vacuoles, and glycogen-rich vacuoles begin to accumulate at the base of the luminal cells and begin to secrete. Eosinophilic bulge in the lumen of the gland During the last 7 days of the secretory phase, stomal changes become prominent and include the following sequential changes: maximum interstitial edema; development of spiral artery hypercolicity; interstitial condensation around the spiral arterioles; interstitial lymphocytic infiltration; and stomas around the spiral arterioles. local necrotic spiral arterioles. NK lymphocytes surround the arterioles and form cell-to-cell connections with stromal cells (King, 2000).

Implantation

The process of implantation occurs where the embryo attaches to the surface of the endometrium and its epithelium. Before implantation occurs, a coordinated process is required between the blastocyst stage embryo and the luteal stage endometrium, which has been prepared and occurs on days 16–22 of the ideal 28-day menstrual cycle. The implantation process consists of three stages: contact of the blastocyst with the endometrial implantation site (apposition), attachment of trophoblast cells of the blastocyst to the receptive endometrial epithelium (adhesion), and invasive trophoblast cells crossing the basement membrane of the endometrial epithelium and invading the endometrial stroma (Kim & Kim, 2017). During the implantation window period, there is a time limit for the blastocyst to be ready to attach to the endometrium, and the implantation process will fail or be defective if this coordination occurs out of phase, and spontaneous abortion may occur. 75% of failed pregnancies are due to implantation failure (Cha, Sun, & Dey, 2019).

CONCLUSION

A good reproductive system is very important for the survival of a living creature or organism. In humans and primates, reproductive success depends on the menstrual cycle of ovulation. The ovulatory menstrual cycle requires the complex and integrated integration of the hypothalamus, pituitary, ovaries, and endometrium. The hypothalamus regulates the pulse through the pulsatile release of GnRH. The pituitary gland translates the pulse set by the hypothalamus into signals to secrete LH and FSH, which control the activity of the ovarian follicles and ovulation. Based on the results of the discussion, there are many factors that influence the occurrence of disturbances in the menstrual cycle which can affect reproductive health, including diabetes, night shift work schedules, nutritional intake, smoking habits, as well as psychological stress and anxiety during a pandemic due to the Covid-19 disease and administration of vaccines. Further research is needed to better understand in more detail the causes of menstrual disorders, especially those related to Covid-19 and its vaccine, and it is necessary to provide education, especially to women of childbearing age about the dangers of cigarette smoke to fertility.

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