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No personality differences between oral contraceptive users and naturally cycling women: Implications for research on sex hormones

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ABSTRACT

The rate of muscle cell growth is also dependent on the activity of some hormones, including growth hormone (GH), insulin, insulin-like growth factor-1 (IGF-1), and steroid sex hormones, especially testosterone. Research results on the acute hormonal response to resistance training show that anabolic hormones such as growth hormone and testosterone, which are very important and vital in tissue growth and remodeling, increase during and after resistance training. These hormones play an important role in increasing protein synthesis. Therefore, the improvement of some physical fitness factors in adolescents is attributed to the increase in the level of these hormones. In this regard, Kramer (2004) stated that if the rest interval between resistance training periods performed at 80% of 1RM in 6 periods and 10 repetitions in each period is less than 1 minute, it can cause a significant increase in the secretion of growth hormone and testosterone. Testosterone is an anabolic hormone that stimulates protein synthesis and plays a very important role in the growth and maintenance of muscle tissue. Growth hormone is one of the most important hormones in the body that, along with a group of other hormones, affects metabolism and is necessary for maintaining body weight and protein synthesis in adults. It has been proven that normal growth is directly related to the plasma concentration of Somatomedin-C or insulin-like growth factor IGF-1. The secretion of GH and IGF-1 is effective in increasing muscle size, and a direct relationship has been observed between the concentration of these hormones and the increase in muscle strength and size.

Introduction

Hormones are a group of chemicals that are produced in very small amounts in the body and have regulatory effects to maintain the normal state of the body. A decrease or increase in the amount of these hormones can cause some important diseases in humans [1]. Hormones are secreted from special glands in the body, sex hormones are mainly made from cholesterol in the gonads (ovaries and testicles) [2].

These hormones are also produced in small amounts in other tissues such as the adrenal glands, placenta, liver, etc. Imbalance of sex hormones leads to various diseases such as precocious puberty, feminization syndromes, infertility, and lack of secondary sexual characteristics. Resistance training is an essential and important component of most exercise programs. These exercises are also very important in rehabilitation programs for athletes after physical injuries [3].

The effectiveness of these exercises in increasing muscle strength, treating sports injuries, and preventing muscle mass loss due to aging and inactivity depends on the volume of training. According to research evidence, high-intensity resistance training, i.e. approximately 80% of one repetition maximum (1RM), causes optimal increases in muscle strength [4].

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It has also been reported that resistance training with 6-12 repetitions and an intensity of 70-85% of 1RM causes increases in muscle strength and size or hypertrophy. The American College of Sports Medicine (ACSM) also recommends resistance training with loads greater than 70% of 1RM for functional and morphological (appearance) adaptations of the muscle [5].

Therefore, one of the main goals of using different resistance training methods is to increase maximum strength and muscle size or hypertrophy. According to the results of the studies, high-intensity training (80-90% of 1RM) with a low number of repetitions (2-8 repetitions) and long rest intervals (2-5 minutes) are suitable for increasing maximum strength, and moderate-to-high-intensity training (70-80% of 1RM) with a high number of repetitions (8-15 repetitions) and shorter rest intervals (30 seconds to 2 minutes) are suitable for increasing muscle size or hypertrophy [6].

However, different results have been reported in the field of short-term and long-term hormonal adaptations related to increasing strength and muscle mass size after different training protocols. Resistance training at 70-80% of 1RM intensity, which has been reported to be an appropriate intensity for increasing muscle strength and size, is also necessary for causing changes in hormones related to increasing muscle strength and size. Therefore, it seems that high-intensity resistance training is accompanied by large changes in anabolic-catabolic hormones [7].

The balance between catabolic hormones such as cortisol and anabolic hormones such as testosterone and dehydroepiandrosterone (DHEA) has an important application in the performance and recovery periods after resistance training. Cortisol is a catabolic hormone and the most important anti-stress hormone in the body, but its increase in the long term causes problems, the most important of which are problems related to the immune system and protein degradation. The results of the studies show that cortisol changes depend on the intensity and duration of training [8].

Estrogen

Refers to a group of hormones including estriol, estradiol, and estrone that are produced in the female body. Estrogens are mainly synthesized in the ovaries, testicles, and adrenal glands from the androgens androstenedione and testosterone. Estrogen is released from the egg during the follicular phase of the normal ovarian cycle. This hormone causes the growth of the female reproductive system and the development of female characteristics, such as breast enlargement in females and a deep female voice [9].

The secretion of this hormone is very low during childhood, and during puberty, its secretion increases, causing the appearance of female sexual characteristics. Estrogens also increase bone formation and cause the distribution of fat in the body to be feminine (mostly in the breasts, hips, and thighs). Estrogen in the uterine wall causes the growth and hyperemia of the endometrium (the inner wall of the uterus) [10].

It also reduces the release of gonadal stimulating hormone in the hypothalamus and reduces the release of FSH and LH from the pituitary gland. After menopause, almost no estrogen is produced in the body. Therefore, bone formation activity in the body is greatly reduced. If this condition is severe, it leads to osteoporosis in postmenopausal women. Estrogen measurement is used in cases of evaluating estrogen levels in patients with abnormal menstrual cycles, abnormally heavy bleeding, examining sexual maturation, infertility, the presence of female characteristics (gynecomastia), monitoring hormone replacement therapy during menopause as a tumor marker (diagnosis of estrogen-producing tumors) and examining ovarian function [11].

Estradiol (17-beta-estradiol)

Estradiol (E2) is produced in the ovaries. Women have a feedback mechanism for this hormone, so that a decrease in E2 levels stimulates the hypothalamus and gonadotropin-releasing factors, which in turn stimulates the pituitary gland to secrete FSH and LH. These hormones stimulate the ovaries and produce E2. The level of this hormone reaches its maximum during the ovulation phase of the monthly cycle. In men, a small amount of this hormone is also produced. About a third of estrogen is produced in the testes and the rest is obtained from the conversion of testosterone and estrone in peripheral tissues [1214]. A large amount of estradiol in serum is bound to albumin and sex hormone-binding globulin (SHBG), and only 2-3% is present in free form.

- ✓ Estradiol is the most abundant estrogen in premenopausal women.
- ✓ Serum estradiol levels vary at different times of the day. Therefore, in repeated tests, samples should be taken at a specific time of day [15].
- ✓ Decreased estradiol levels are seen in ovarian failure, Turner syndrome, hypothyroidism, Stein-Loenthal syndrome, menopause, anorexia nervosa, polycystic ovary syndrome, hypopituitarism, and hypogonadism.
- ✓ Increased estradiol levels are seen in ovarian, testicular, and adrenal tumors, precocious puberty in women, gynecomastia (feminine syndrome in men), and liver necrosis and cirrhosis.
- ✓ Birth control pills and clomiphene cause decreased serum E2 levels [16].
- ✓ Adrenocorticosteroids, ampicillin, estrogen-containing drugs, phenothiazines,

and tetracyclines may cause increased E2 levels.

- ✓ Levels of the female hormone progesterone increase steadily in the early weeks of pregnancy, causing the cervix to thicken and mucus to form. As HCG levels rise, the production of estrogen and progesterone hormones increases, and early pregnancy symptoms such as nausea, vomiting, and frequent urination will appear [17].
- ✓ Female hormone levels continue to rise in the second trimester of pregnancy. During this period, placental cells produce the hormone human placental lactogen (HPL) to regulate the mother's metabolism and nourish the growing fetus. As pregnancy ends, female hormone levels decrease and gradually return to pre-pregnancy levels.

The Role of Female Hormones in Menopause

The average age of menopause in women is 52. During this time, ovarian function declines and the production of estrogen and progesterone drops sharply. This period is usually accompanied by a period called perimenopause, when a person experiences their last menstrual cycle [18-20].

Previous Studies

A new study found that women who take birth control pills have a smaller hypothalamus, a key brain region, compared to women who don't take the pill, researchers found in a new brain study. The study was recently presented at the annual meeting of the Radiological Society of North America (RSNA) [21].

The hypothalamus, located in the brainstem and above the pituitary gland, produces hormones and helps regulate basic body functions, including body temperature, mood, appetite, libido, sleep cycles and heart rate. The structural effects of sex hormones, including oral contraceptives, on the human hypothalamus have not been reported before, the researchers said. This may be because validated methods for quantitative analysis of hypothalamic MRI scans are not available [22].

"There is a dearth of research on the effects of oral contraceptives on this small but essential part of the living human brain," said Michael L. Lipton, MD, professor of radiology at the Gruss Magnetic Resonance Research Center at Albert Einstein College of Medicine and medical director of MRI services at Montefiore Medical Center in New York City.

"We developed validated methods for assessing hypothalamic volume and confirmed for the first time that current oral contraceptive use is associated with smaller hypothalamic volume." Oral contraceptives are among the most popular birth control pills and are also used to treat a variety of conditions, including irregular menstruation, cramps, acne, endometriosis and polycystic ovary syndrome [23].

According to a 2018 report from the National Center for Health Statistics of the Centers for Disease Control and Prevention, from 2015 to 2017, approximately 47 million women aged 15-49 in the United States reported using birth control pills. Of those, 12.6 percent were taking the pill. In their study, Dr. Lipton and her colleagues recruited a group of 50 healthy women, 21 of whom were taking oral contraceptives [24].

All 50 women underwent MRI scans of the brain, using a validated method to measure the volume of the hypothalamus. “We found significant differences in the size of brain structures between women who took oral contraceptives and women who did not take them,” said Dr. Lipton. “This preliminary study suggests a strong association and encourages further research to investigate the effects of oral contraceptives on brain structure and their possible impact on brain function.” Other findings from the study, which Dr. Lipton described as preliminary, were that smaller hypothalamic volume was also associated with greater anger and showed a strong correlation with symptoms of depression. However, the study found no significant relationship between hypothalamic volume and cognitive function [25-27].

The role of female hormones in libido

Female hormones such as estrogen, progesterone and testosterone all affect women's libido. If estrogen levels are too high in a woman's body, their libido increases sharply, but too high progesterone levels in a woman's body cause a decrease in libido. Some research shows that decreased testosterone levels in a woman's body cause a decrease in libido. Doctors usually do not consider testosterone therapy appropriate in such conditions due to side effects such as weight gain, hair loss, clitoral enlargement and increased body hair.

The status of female hormones such as estrogen and progesterone can be improved by following a healthy lifestyle, eating the right foods and managing stress. If you are looking to naturally boost female hormones, consider the following:

- ✓ Eating fiber-rich foods such as fruits, vegetables, legumes, and whole grains.
- ✓ Quit smoking [28].
- ✓ Drink plenty of water and stay hydrated.
- ✓ Take supplements containing B-complex, vitamin D, magnesium, and zinc.
- ✓ Eating plant sources rich in estrogen, such as soybeans, chickpeas, and lentils.
- ✓ Eating essential fatty acids such as omega-3, olive oil, and fish.
- ✓ Exercising regularly daily.
- ✓ Managing stress.
- ✓ Getting enough sleep [29].

- ✓ Reducing your intake of artificial sugars and refined carbohydrates.
- ✓ Avoiding processed foods and foods containing trans fats.
- ✓ Avoiding alcohol and caffeine [30].

What are female hormone regulating drugs?

Female hormone regulating drugs are usually prescribed with the aim of balancing the levels of hormones in the body and resolving problems caused by hormonal disorders [30]. The doctor usually determines the type of drug according to the patient's specific condition and the severity of the hormonal disorder. In the table below, we introduce the most important drugs used to regulate female hormones:

Table 1. Type of female hormone-regulating drug

Type of female hormone-regulating drug	Description
Estrogen pills	It is prescribed to relieve hot flashes and menopausal symptoms caused by decreased estrogen.
Birth control pills	In addition to regulating female hormones, it helps regulate the menstrual cycle and treat acne, or prevent unwanted hair growth.
Anti-androgen drugs	It helps reduce symptoms of increased male hormones in women.
Thyroid drugs	Hypothyroidism is one of the reasons for the disruption of female hormone regulation, which uses synthetic hormones to balance thyroid hormone levels.
Metformin pills	Some doctors use this pill to treat insulin resistance in patients with polycystic ovary syndrome.

Discussion

The role of sex hormones in menstruation

The first time a person menstruates, usually between the ages of 12 and 13. However, menstruation can occur at any time between the ages of 8 and 15. After menstruation, many people have regular menstrual cycles until they reach menopause. Menstrual periods usually last about 28 days, but can vary between 24 and 38 days. The menstrual cycle occurs in three phases that coincide with hormonal changes:

1- Follicular phase: The first day of your period marks the beginning of a new menstrual cycle. During your period, blood and uterine tissue are shed from your body through your vagina. Estrogen and progesterone levels are very low during this phase, which can cause irritability and mood swings. The pituitary gland also releases FSH and LH, which increase estrogen levels and signal the growth of follicles in the ovaries. Each follicle contains an egg. After a few days, a dominant follicle appears in each ovary [31]. The ovaries will absorb the remaining follicles. As the dominant follicle continues to grow, it produces more estrogen. This increase in estrogen triggers the release of endorphins, which increase energy levels and improve mood. Estrogen also thickens the endometrium, the lining of the uterus, to prepare for a possible pregnancy.

2- Ovulation Phase: During the ovulation phase, estrogen and LH levels in the body peak, causing the follicle to burst and release the egg from the ovary. An egg can survive for about 12 to 24 hours after it leaves the ovary. Fertilization of the egg only occurs during this time [32].

3- Luteal Phase: During the luteal phase, the egg travels from the ovary through the fallopian tube to the uterus. The ruptured follicle releases progesterone, which thickens the lining of the uterus, preparing it to receive a fertilized egg. When the egg reaches the end of the fallopian tube, it attaches to the uterine wall. The unfertilized egg causes estrogen and progesterone levels to drop. This marks the beginning of the week before menstruation. Eventually, the unfertilized egg and uterine lining are shed, marking the end of the current menstrual cycle and the beginning of the next [33].

Pregnancy begins the moment a fertilized egg implants in the lining of the uterus. After implantation, the placenta begins to grow and begins producing a number of hormones, including progesterone and human chorionic gonadotropin (hCG). Progesterone levels rise steadily during the first few weeks of pregnancy, causing the cervix to thicken and a mucus plug to form. The increased levels of hCG in the body stimulate the production of more estrogen and progesterone. This rapid increase in hormones leads to early pregnancy symptoms such as nausea, vomiting, and the need to urinate more. Estrogen and progesterone levels continue to rise in the second trimester of pregnancy.

At this time, placental cells begin to produce a hormone called human placental lactogen (HPL). HPL regulates a woman's metabolism and helps nourish the growing fetus. As pregnancy ends, hormone levels decline and gradually return to pre-pregnancy levels [34].

The Role of Sex Hormones in Menopause

Menopause occurs when a person stops menstruating and is no longer able to get pregnant. In the United States, the average age at which a woman experiences menopause is 52. Symptoms of perimenopause can include:

- ✓ Irregular menstrual periods.
- ✓ Hot flashes.
- ✓ Sleep problems.
- ✓ Mood swings.
- ✓ Vaginal dryness.

According to some sources, perimenopause usually lasts about 4 years, but it can last anywhere from 2 to 8 years. A person reaches menopause when they have gone a full year without a period. After menopause, the ovaries produce only very small but steady amounts of estrogen and progesterone. Low estrogen levels can reduce a person's libido and cause bone loss, which can lead to osteoporosis. These hormonal changes can also increase the risk of heart disease and stroke [35].

Role of Sex Hormones in Sexual Desire and Arousal

Estrogen, progesterone, and testosterone all affect sexual desire and arousal. Having higher levels of estrogen in the body can soften the vagina and increase sexual desire. Increased progesterone can reduce sexual desire. There is some debate about how testosterone levels affect a woman's libido. Low testosterone levels may lead to a decreased libido in some women. However, testosterone therapy appears to be ineffective in treating low libido in women. Testosterone therapy can increase the effects of estrogen, according to a study, but this can lead to unwanted side effects. For the first time, a male contraceptive pill without the use of hormones has entered clinical trials [36].

A drug that could open a new chapter in family planning and birth control. The drug, called YCT-529, has already shown promising results in animal tests, including mice and monkeys. The researchers say the pill has been able to significantly reduce sperm production without causing serious side effects. In male mice, the drug began to work in less than a month and in the cases tested, it reduced the chance of pregnancy in the female partner to almost zero. In monkeys, a rapid decrease in sperm count was also observed at higher doses, without any serious negative effects on the animal's overall health [37].

The scientists say that the most important point of the new method is that fertility quickly returns to normal after stopping the drug. There was also no change in the levels of three key hormones associated with fertility during use. This distinguishes it from previous types of male contraceptives that were based on hormonal manipulation [38].

Male sperm Photo (Canva)

"A safe and effective pill for men could provide new options for couples and divide the responsibility for family planning more equitably between men and women," says Dr. Gunda Georg, a medicinal chemist at the University of Minnesota and one of the main researchers on the project. The drug disrupts the process of cell growth and sperm production by specifically affecting the retinoic acid receptor in the body, and by focusing on only one version of this receptor, it reduces the likelihood of side effects [39].

The project, funded by the US National Institutes of Health, is the result of a joint collaboration between scientists at the University of Minnesota, Columbia University and the pharmaceutical company UrChoice. According to Nadia Manowitz, founder and chief scientific officer of UrChoice, the animal studies have provided a solid foundation for the start of human trials. The first phase of the drug's clinical trial has been completed and it has now entered the second phase. The phase that examines the drug's safety and efficacy. This phase begins in September 2024 in New Zealand [40].

Scientists say: The development of the drug Canva, although slower than initially expected, is still moving in a positive direction. In addition to YCT-529, other studies are underway in the field of non-hormonal methods of male contraception. Among them is the drug CDD-2807, which has prevented fertilization in mice, but has not yet entered the human phase. The last time a male contraceptive was officially approved was in the 1980s, when a painless, nonsurgical procedure called a vasectomy was introduced. Now, with unintended pregnancy rates approaching 50 percent in some countries, experts are stressing the urgent need to develop more options for men [41].

Dr. Manutz said: "Women have long shouldered the burden of contraception alone. The data shows that men are willing to take on more of the burden, and women trust them. After nearly two hundred years of inaction on male contraception, it's time for a change. Hormonal contraceptives have been shown to make some people feel anxious. However, for some, they are associated with a reduction in anxiety symptoms [42]. A 2004 study found that users of hormonal contraceptives had higher levels of anxiety than others [43].

Another 2018 study found that using an IUD containing the hormone levonorgestrel increased anxiety levels. However, a 2013 study of women in the United States found that the drugs reduced depression levels in young women. Progesterone-only pills appear to be more associated with

depression and anxiety than other birth control options [44].

Conclusion

Female hormones play an important role in the biological function and various stages of women's lives, including puberty, menstruation, pregnancy, and menopause. These hormones are considered the most important factors in ensuring women's health by regulating the menstrual cycle, maintaining pregnancy, supporting fetal growth, and moderating the physical and psychological changes associated with menopause. Disruption of the balance of female hormones can lead to problems such as menstrual disorders, infertility, and skin problems. Early identification of these problems and their proper management through a healthy lifestyle, proper nutrition, and, if necessary, the use of drugs that regulate female hormones can prevent more serious problems. Many prescription and over-the-counter medications can reduce sexual desire and affect sex life. Medications can affect sexual desire in two ways. Some medications cause symptoms that make sex more difficult. For example, medications that because vaginal dryness may be painful for women, resulting in decreased sexual desire. Similarly, drugs that affect blood flow to the penis can cause erectile dysfunction, which affects sexual desire. In addition, some drugs can reduce sexual desire by affecting sex hormones. These hormones play essential roles in sexual development, sexual desire, and the regulation of other components of the reproductive system. There have been numerous studies on the effect of growth hormone on increasing maximum strength and increasing muscle size, most of which have shown a direct relationship between the concentration of this hormone and the increase in muscle strength and size. In adults, growth hormone facilitates protein synthesis. This action is carried out by transporting amino acids across the cell membrane, which leads to the stimulation of increased production and activation of cellular ribosomes. Another variable that is dependent on muscle cell size is the IGF-1 hormone. The IGF system is a family of peptides and proteins that play a central role in growth and metabolism. IGF-1, as the most important member of this family, exerts strong growth effects on muscle and bone tissue. This peptide also mediates insulin-like actions, particularly in muscle tissue, and circulates in plasma bound to one of its six binding proteins. Evidence suggests that there is a feedback-regulatory relationship between growth hormone and the IGF-1 system, whereby growth hormone secretion increases hepatic production of IGF-1. In addition to these specific effects, IGF-1 mediates some of the actions of GH, particularly in muscle and bone tissue, and circulating IGF-1 levels inhibit GH secretion in a negative feedback manner. Researchers believe that GH participates indirectly in stimulating growth. Thus, GH causes the liver, and to a much lesser extent other tissues, to produce several small proteins called somatomedins, which have a very strong effect on increasing the growth aspects of tissues. GH travels through the bloodstream to the liver and other peripheral tissues, where IGF-1 is produced. This hormone has anabolic effects and promotes tissue growth.

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Authors' Contributions

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