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Effect of Female Sex Hormones on Cardiorespiratory System: Theoretical Review

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Abstract
This study aimed at analyzing the effect of the female sex hormones upon the cardiorespiratory system. And the results showed that the cardiac output measurement showed no significant increase during both phases of menstrual cycle before exercise but there was an insignificant increase soon after exercise owing to sympathetic over activity. The observed increase in the peripheral blood flow during mid-follicular phase before and after exercise revealed that influence of estrogen increases the arterial distensibility. The observed increase in the respiratory efficiency test during early luteal phase before and soon after exercise revealed the influence of progesterone, which is considered to be a potent stimulator of respiration, and added up effect of hormones and exercise-induced changes.

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1.1 Introduction

Hormones are secreted into the bloodstream and control most major bodily functions, they act as the body's messengers. Hormones are vital to a person's health, however, as the human being age, hormone production progressively decreases. Synthetic hormones are often prescribed by doctors in an attempt to restore the body's hormonal balance. Unfortunately, synthetic hormones also produce undesirable effects such as weight gain, bloating, headaches, fatigue, heart disease, and possibly cancer. On the other hand, bioidentical hormones, an alternative to commonly prescribed synthetic hormones, are natural hormones identical to those produced by the body itself. Since they are natural and identical in structure to those produced by the body, they allow the body to function at an optimal level as instructed by hormones without negative side effects. Along with a healthy diet and exercise and nutritional supplements a person's body can be restored to hormonal balance and wellbeing (McArdle, Katch & Katch, 2010).

The first record of the term "hormesis" in scientific publications is found in the 1943 article by Southam and Ehrlich "Effects of extract of western red-cedar heartwood on certain wood-decaying fungi in culture". The authors investigated the effects of a wide concentration range of an anti-fungal agent, finding that despite high concentration decreased the fungus growth, doses below the growth-inhibitory threshold actually stimulated it (Southam & Ehrlich, 1943).

Although debated due to initially limited experimental evidence, the concept has been successively established as a relevant model for explaining the biological effects of certain substances (Calabrese, 2010).

Another controversial subject during recent years is the menopausal hormone therapy debate. The effects of estrogens on stroke have been especially conflicting, since large epidemiological studies and numerous animal studies have found hormone therapy to be neuroprotective, while, on the contrary, the randomized controlled trial Women's Health Initiative (WHI) reported increased stroke risk and some animal studies have demonstrated increased ischemic lesions. Recent evidence indicates that estrogens' effects in rat stroke models may obey hormetic principles, so that physiological concentrations are protective while higher, prolonged concentrations are detrimental (Strom, Theodorsson, Holm & Theodorsson, 2010).

Hormones are internal messenger chemicals in the body. They are released by special cells into the blood stream, in varying amounts that depend on how much activity is called for at each time. Hormones circulate through the body and regulate the activity and growth of cells and organs by stimulating or inhibiting specific functions (Roberts, 2007).

The most widely recognized examples of hormones are the sex hormones estrogen and testosterone, as well as adrenaline, which is the hormone that increases strength and energy to prepare the body for action. However, numerous other hormones also play varied roles in ensuring the normal functioning of the human body (Sherwood, 2015).

There are indications that sex hormones, and in particular estrogen and progesterone, influence irritable bowel syndrome. Receptors for these hormones have been found on gastrointestinal cells, which suggest that the gastrointestinal tract is designed to sense and react to them. There is also evidence that such reactions do indeed occur: Both women with and without IBS tend to experience systematic changes in gastrointestinal symptoms at the times in their menstrual cycle when the amounts of these hormones in the blood change most (Adeyemo, Spiegel & Chang, 2010).

Symptoms such as stomach pain, diarrhea, nausea, and bloating are generally greatest during menses, when estrogen and progesterone drop down to the lowest levels in the body. Bloating is the only IBS-type symptom which also seems to be worse during the second half of the cycle (the luteal phase) before the beginning of menses (Heitkemper & Chang, 2009) .

The Cardiorespiratory system is responsible for the following functions within the human body:

1- Moving oxygenated blood from the lungs to the body, while at the same time moving de-oxygenated blood from the body back to the lungs via the heart.
2- Distributing the key nutrients to the cells around the body at the required rate. This takes place during exercise or rest.
3- Removing metabolic waste products such as Carbon Dioxide, Lactic Acid and Urea.
4- Regulation of blood PH balance to control acidosis or alkalosis.
5- Transporting hormones and enzymes to regulate physiological and psychological functions.
6- Maintaining fluid volume to prevent dehydration.
7- Maintaining body temperature by absorbing and redistributing heat through blood flow to the skin.

1.2 Sex hormones

The ovary produces three classes of sex steroids: estrogens (see figure 1), progestins(see figure 2) and androgens(see figure 3). Production of sex hormones fluctuates with ovarian activity. Hormonal fluctuations in the menstrual cycle include increasing 17b-estradiol (E2), but low progesterone plasma concentrations in the follicular phase, and high plasma 17b-E2 and progesterone concentrations in the luteal phase.

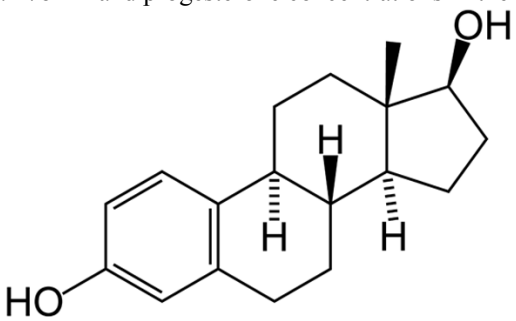

Figure (1): Chemical formula of the estrogens

If pregnancy occurs, luteolysis is prevented and 17b-E2 and progesterone levels remain high. Later in life (menopause), with the depletion of follicles, sex hormone concentrations drop to very low levels.

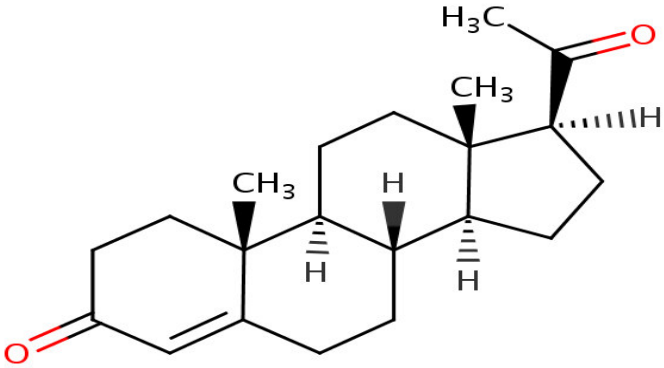

Figure (2): Chemical formula of the progestins

In oral contraceptive (OCC) users, the progestin component suppresses luteinizing hormone secretion, while the estrogenic component suppresses FSH secretion preventing selection and emergence of a dominant

follicle and ovulation. Therefore, naturally 17b-E2 and progesterone plasma concentrations are low during OCC use, however, at the end of the pill free period the 17b-E2 concentration is comparable with the concentration, which characterizes the early follicular phase (Bouman, Heineman & Faas, 2005).

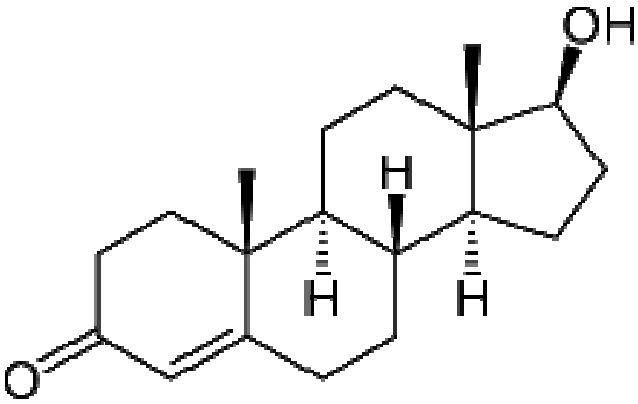

Figure (3): Chemical formula of the androgens

1.3 Cardiorespiratory system

The blood circulatory system in the human body (the cardiovascular system) delivers nutrients and oxygen to all cells in the body. It consists of the heart and the blood vessels running through the entire body. The arteries carry blood away from the heart; the veins carry it back to the heart. The system of blood vessels resembles a tree: The "trunk," the main artery (aorta), branches into large arteries, which lead to smaller and smaller vessels. The smallest arteries end in a network of tiny vessels, the capillary network. There is not only one blood circulatory system in the human body, but two, which are connected:

The systemic circulation provides organs, tissues and cells with blood so that they get oxygen and other vital substances. The pulmonary circulation is where the fresh oxygen we breathe in enters the blood. At the same time, carbon dioxide is released from the blood.

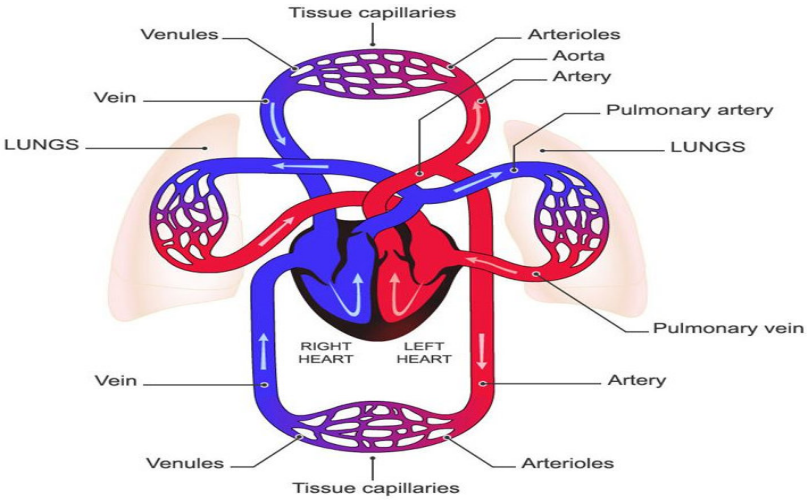

Figure (4): The cardiorespiratory system

Blood circulation starts when the heart relaxes between two heartbeats: blood flows from both atria (the upper two chambers of the heart) into the ventricles (the lower two chambers) which then expand. The following phase is called ejection period, which is when both ventricles pump the blood into the large arteries.

In the systemic circulation, the left ventricle pumps oxygen-rich blood into the main artery (aorta). The blood travels from the main artery to larger and smaller arteries into the capillary network. There the blood releases oxygen, nutrients and other important substances and takes on carbon dioxide and waste substances. The blood, which is now low in oxygen, is now collected in veins and travels to the right atrium and into the right ventricle.

Now pulmonary circulation starts: The right ventricle pumps blood that carries little oxygen into the pulmonary artery, which branches off into smaller and smaller arteries and capillaries. The capillaries form a fine network around the pulmonary vesicles, grape-like air sacs at the end of the airways. This is where carbon dioxide is released from the blood into the air contained in the pulmonary vesicles and fresh oxygen enters the bloodstream. When we breathe out, carbon dioxide leaves our body. Oxygen-rich blood travels through the

pulmonary vein and the left atrium into the left ventricle. The next heart beat starts a new cycle of systemic circulation (Chiras, 2012).

1.4 The menstrual cycle and hormonal contraceptives

Assuming a regular 28-day cycle, the levels of sex hormones in the female body fluctuate according to the following pattern, while levels of testosterone are virtually constant (Buser, 2009):

Phase 1: Menstrual phase (days 1-5 of the cycle): secretion of oestrogen and progesterone ceases.

Phase 2: Follicular phase (days 6-12): oestrogen levels increase gradually, there is virtually no progesterone.

Phase 3: Peri-ovulatory phase (days 13-15): oestrogen levels decrease, there is still little progesterone.

Phase 4: Luteal phase (days 16-23): progesterone is secreted in large quantities, oestrogen levels reach a second peak.

Phase 5: Premenstrual phase (days 24-28): both oestrogen and progesterone levels decline drastically during this phase.

For subjects experiencing a natural menstrual cycle, we construct five binary variables indicating in which phase of the menstrual cycle a subject is situated (assuming a regular 28-day cycle). We also construct two continuous variables representing the expected oestrogen and progesterone levels given the day of the cycle a subject is currently in (Apicella, Coren, Anna Dreber, Campbell, Peter, Moshe & Anthony, 2008).

Assuming a regular 28-day cycle can be expected to lead to some measurement error when dividing subjects into the five menstrual cycle phases. However, most of the variability in cycle length between individuals stems from differences in the length of the follicular phase. The length of the ovulatory, luteal, and premenstrual phases on the other hand is relatively fixed (Hampson and Young, 2008). We construct a prospective measure of the menstrual cycle - i.e. we elicit information about the expected beginning of the next menstruation and then count backwards - and the only distinction potentially affected by mis-classification should therefore be the one between the first and second phase. We also ask subjects whether they are currently menstruating or not and use this information to reallocate them between phases one and two, moving all menstruating subjects to phase one and all non-menstruating subjects to phase two. This should eliminate the mis-classifications. Our assessment of expected daily hormone levels should hardly be affected at all as levels of both oestrogen and progesterone are almost constant over the first nine days of the cycle

1.5 Female sex hormones and the cardiorespiratory system

Menstruation involves a cyclic expulsion of sanguineous fluid and a sloughing of uterine wall in a female and is a typical feature of the reproductive cycle in humans and subhuman primates. It is under the control of complex neuro-hormonal influences. Menstruation in most women occurs at regular intervals of 28 days on an average, although most women questioned gave a history of regular intervals of (28 to 30 days), and only (10%–15%) of women were found to show cycle at the precise (28 ± 2) days intervals when menstrual calendar was utilized. In normal adult women, the plasma levels of estrogen vary in different phases of ovarian cycles. There are two peaks of estrogen secretion. The first occurs just before the ovulation (12–13th) day of menstrual cycle, which is termed estrogen surge, and the second peak occurs in the mid-luteal phase.

During the follicular phase of menstrual cycle, the plasma concentration of progesterone is very low about 0.9 ng/mL, and in mid-cycle, its level starts rising owing to secretion from the granulose cells. Progesterone level reaches its peak value of (18 ng/mL) during luteal phase, and its level fall to a minimum value toward the end of the cycle. Estrogen affects systemic and local vasodilation (Anitha, 2016).

Estrogen receptors are found on the artery walls. These receptors on stimulation lead to vasodilatation by the endothelial synthesis of nitric oxide (NO) and prostacyclin (PGI2), which are strong vasodilating agents, and result in altering the endothelial production of endothelin, a strong vasoconstriction agent (Polderma, Stenhouwer, Van Kamp, Dekker, Verheugt & Gooren, 1993).

Finally, estrogen also seems to have blocking effect on calcium channels of the arterial wall, resulting in vasodilatory changes in action and production of these vasoactive substances, which could be responsible for some vasomotor and pressure changes observed in woman during menopause (Chester, Jiang & Sarrel, 1993).

In the luteal phase, the arterial wall stiffening was observed, which was related to a decrease in the flow-dependent endothelial dilatation of the radial artery, as evaluated by the hyperemia after short-term ischemia of the hand. Thus, the variations in radial artery dispensability are typical in the natural menstrual cycle. However, it is likely that the estrogen-dependent decrease in vascular smooth muscle tone causes the larger arterial dispensability of the ovulatory phase, whereas vascular smooth muscle contraction owing to endothelial destruction, resulting in not only a decrease in estrogen level but also in an augment in progesterone and antidiuretic hormone (ADH) levels, leads to the arterial stiffening of the luteal phase (Giannattasio, Mangoni, Faillia, Garage, Stella & Stfaneni, 1996).

Estrogen supposedly increases the basal release of NO, which is a potential vasodilating substance. In this perspective, nitrate and nitrite levels (metabolites of NO) in serum augmented during the early to late follicular

phase of menstrual cycle, in concurrent with the increase in 17 β-estradiol levels (Roselli, Imthurm, Macas, Keller & Dubey, 1994).

Moreover, luteal phase of the menstrual cycle have shown greater resting values of circulating plasma norepinephrine, during which increased levels of both estrogen and progesterone were observed, which offers additional evidence that both of these hormones exhibit efficiency to impart vascular regulations. It's probable that progesterone or any other altered host factors during the period of the menstrual cycle can counteract against the effect of increased estrogen or vascular responsiveness. A vasodilatory effect of estrogen was reported by Meyer et al., who found that E2 administration increased vessel diameter and significant reduction in the radial artery resistance from menses to the follicular phase. In the follicular phase, the endometrium exhibited vascular neoangiogenesis. The influence of estrogen to promote vasodilatation appears in large partly because of its effect to promote NO synthase activity in the peripheral vasculature. The endurance time for fatiguing isometric contractions was about one-third longer in women than in men, when contractions were sustained at 40% of each individual's maximum strength. A sinusoidal variation in endurance occurs 7 to 10 days, after the onset of bleeding. Progesterone is known to stimulate pulmonary ventilation. Female subjects constantly experience a wide fluctuation in estrogen and progesterone levels during their menstrual cycles. Earlier studies have recorded that female sexual hormones affect respiratory function, in particular progesterone, which, during luteal phase, could enhance ventilatory response at rest. Resting minute volume (VE) has been documented to be higher (2.3 L/min or equivalent to 7.07 vs. 6.72 L/min) during the luteal phase when compared with the follicular phase. The associations noted between sexual hormones and respiratory control variables and respiratory muscle function advocate a positive effect of sexual hormones regulating the thoracic pump muscles in the luteal phase. Da Silva et al. evaluated the Spiro metric and respiratory static pressures of 17 young female subjects at bi-weekly intervals for three consecutive menstrual cycles to determine if respiratory function and Spiro metric flow and capacity changed throughout the follicular, preovulatory, and early to mid-luteal phases. The menstrual cycle and individual cycle phase exhibited a noteworthy effect on peak expiratory flow and respiratory static pressures. In the luteal phase, reduction in NO-dependent variation of arterial diameter proposes that a rise in smooth muscle contraction could also initiate from endothelial malfunction.

In a study conducted by Godbole, Joshi & Vaidya (2016), using a cross-sectional methodology; participants were 100 female medical students in the age group of 17–22 years. The Institutional Ethical Committee approval was obtained for the study.

Female medical students having regular menstrual cycle (24–35 days) were included in the study. Females with irregular menstrual cycles, those having any systemic disease, and those undergoing hormone therapies were excluded from the study.

Weight, resting pulse rate, respiratory rate, and VO_2 max were measured during premenstrual phase (20^{th}–25^{th} day) and postmenstrual phase (5^{th}–10^{th} day) for consecutive three cycles. All parameters were recorded at 8.30 a.m. before breakfast.

After recording resting pulse rate and respiratory rate, VO_2 max was measured by Queen's College step test as follows.

1- Participants were asked to step up and down on a bench of 33 cm height at a rate 22 steps/min. This exercise was continued for 3 min. Five seconds after stopping exercise, pulse rate was measured for 15 s and was computed for 1 min (post exercise pulse rate), and with the help of the following formula, VO_2 max was calculated: VO_2 max (ml/kg/min) = 65.81− (0.1847 × post exercise pulse rate)
2- All parameters were recorded for three cycles. Average readings of the three cycles were taken for statistical analysis.

Table 1 shows weight, pulse rate, and respiratory rate values during pre- and post-menstrual phases in the study group. It was observed that there was a significant increase in body weight, pulse rate, and respiratory rate during premenstrual phase.

Table (1): Comparison of weight, resting pulse rate and respiratory rate in premenstrual and postmenstrual phase in study group

Parameter (n=100)	Premenstrual Phase	Postmenstrual Phase	t Value	P Value
Weight in kgs (Mean±SD)	56.09±10.10	55.40±10.24	4.25	<0.001*
Resting pulse rate per min (Mean±SD)	80.77±4.82	78.16±5.26	4.71	<0.001*
Respiratory rate per min (Mean±SD)	18.60±1.84	17.97±1.79	2.95	<0.01*

* Statistically significant

In their study, Godbole, Joshi & Vaidya (2016), findings are similar to the study conducted by Lebrun *et al*. They have also found that there was a decrease in VO_2 max in premenstrual phase compared to postmenstrual phase. Girija and Veeraiah have also documented similar results. Postmenstrual phase is estrogen dependent, and premenstrual phase is progesterone dependent. We have obtained readings showing better oxygen consumption in postmenstrual phase which indicates that estrogen has some favorable effect on oxygen consumption and progesterone must be having some unfavorable effect on the same. Probably estrogen-progesterone ratio must be an important factor deciding maximum oxygen consumption. Progesterone causes more fluid retention on its own. It also activates renin-angiotensin system, thereby increasing plasma volume and leading to hemodilution. Thus, it probably decreases oxygen carrying capacity and therefore must be responsible for decrease in oxygen consumption by muscles. Increased plasma volume brought about by progesterone can increase load on heart temporarily and can reduce its performance.

Progesterone increases minute ventilation. The seat of action of progesterone is thought to be either on respiratory centers or on peripheral chemoreceptors or a combination of both. This may result in more consumption of energy by respiratory muscles that are otherwise available for other muscular activities. Increased minute ventilation may give greater feeling of breathlessness to the individual which may reduce exercise performance (Thomas, 2003).

Increase in circulating blood volume due to fluid retention and thermogenic action of progesterone after ovulation could be the reason for increase in pulse rate during premenstrual phase. Similar findings were noted by Christina *et al*. and Olayaki *et al*. However, Hirshoren *et al*. have found no effect of the sex hormones on the heart rate in different phases of the menstrual cycle.

Increase in respiratory rate during premenstrual phase could be due to progesterone as it stimulates respiration by acting on respiratory centers and also through peripheral chemoreceptors. Similar results were observed by Sunyal *et al*. and Bandyopadhyay and Dalui. Bayliss *et al*. have reported that this action of progesterone is mediated through steroid receptors in the central nervous system.

In the present study, we have found that values of maximum oxygen consumption (VO_2 max) in premenstrual phase were decreased as compared to postmenstrual phase.

Redman *et al*. studied the effects of synthetic progestins on the fitness status of young sedentary women. There was a significant effect on exercise status in different phases of menstrual cycle possibly through an effect on stroke volume and a shift in the principal energy substrate used during exercise from carbohydrate to lipid.

1.6 Respiratory Changes

During follicular phase, the readings were not much increased at resting level but increased insignificantly after exercise, which indicates that respiratory minute volume increases linearly with work followed by an increase in the pulmonary blood flow and the perfusion of alveoli, leading to an improved breathing capacity and VO2 max. But, during luteal phase, the subjects were observed to have improved respiratory efficiency even at resting stage. The major findings of this study suggests that menstrual hormones did not affect breathing responses at rest; submaximal and maximal exercise showed comparable results, which suggested that forced vital capacity and forced expiratory volume and their ratio were not affected by phases of the menstrual cycle. On the basis of these data, our result support that there was a positive correlation between the ventilation and the progesterone hormone during early luteal phase compared with mid-follicular phase before and after exercise.

1.7 Conclusions

Cardiac output measurement showed no significant increase during both phases of menstrual cycle before exercise but there was an insignificant increase soon after exercise owing to sympathetic over activity. The observed increase in the peripheral blood flow during mid-follicular phase before and after exercise revealed that influence of estrogen increases the arterial distensibility. The observed increase in the respiratory efficiency test during early luteal phase before and soon after exercise revealed the influence of progesterone, which is considered to be a potent stimulator of respiration, and added up effect of hormones and exercise-induced changes. The findings of this research study will be useful for women in various phases of menstrual cycle, during the performance of strenuous exercise, which requires an appreciable cardiac reserve.

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