

# By What Mechanism Does Stress Affect Ovulation?

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## Abstract

*This paper explores the many mechanisms of how stress influences ovulation. For ovulation to occur, there needs to be a series of hormones released in a specific order, and in a specific amount. This paper will discuss the various type of stress a person can experience, and which specific reproductive hormone each different type of stress disrupts. This paper will also bring proof as to how each hormone is disturbed, and by which mechanism it is disrupted. There has not been one main mechanism that has been found thus far, therefore, it is important to take into consideration the various routes that stress can take to disturb ovulation. Understanding the various mechanisms is important in finding a way to treat women with menstrual or ovulatory dysfunction.*

## Introduction

Stress plays an important role in the daily life of a healthy person. Stress can elicit biological and emotional responses which may affect the female's hormones, leading to change in the menstrual cycle, and ovulation. Ovulation is the release of an oocyte from the ovary. For ovulation to occur, a sequence of events must happen. The hypothalamus will secrete gonadotropin releasing hormone (GnRH), which stimulates the adenohypophysis to secrete both follicle stimulating hormone (FSH) and luteinizing hormone (LH). The levels and timing of these secretions is controlled by GnRH, and other factors such as inhibin and activin (Hawkins, Matzuk, 2008). The gonadotropins then stimulate the ovary to produce the steroid hormones estrogen or progesterone, as well as other peptides. Adequate presence of FSH stimulates the follicles in the ovary to grow even more and become competent to develop into an antral follicle. When it is exposed to LH, it produces estrogens from androgenic precursors. The concomitant increase in FSH on the follicular cell results in more binding of FSH and greater amount of estrogen secretion, resulting in a very high estrogen environment. Once high estrogen levels are triggered, a message is sent to the anterior pituitary to induce the LH surge, which leads to ovulation, when it picks a dominant follicle (Hawkins, Matzuk 2008). These mechanisms occur in a normal, healthy functioning female with normal hormone levels. However, when a female is exposed to stress, whether it is physical or mental, her hormones may not be at normal levels, thus her menstrual cycle and her ovulation mechanism may be disrupted. This paper will explore the effects of stress on mechanism in ovulation, and specifically, which hormones it disrupts when a female is exposed to a variety of different types of stress.

## Method

The research obtained about the mechanism of how stress affects ovulation was collected from a variety of sources. The majority of the articles were collected using Touro's library to access databases such as Proquest, Pubmed, and many more. Other articles were also found through google scholar. After reviewing and studying many articles on the topic, there was adequate evidence to answer the research question.

## The Impact of General Stress on The Reproductive System

There is a direct biological relationship between stress and the reproductive system, where stress activates a part of the body called

the HPA Axis- the Hypothalamic-Pituitary-Adrenal axis, which is the central stress response system. When a person is under stress, the HPA axis is activated, and there are increased levels of cortisol and corticotropin-releasing hormone. The cortisol and corticotropin releasing hormone has the ability to suppress the normal levels of the reproductive hormones, which can potentially lead to abnormal ovulation, anovulation and amenorrhea (Biller, et al 1990). This paper will explore exactly which hormones the HPA axis acts upon in order to interfere with ovulation.

When there is a presence of adequate estrogen levels and there is stress-induced activation of the HPA axis, a significantly higher amount of LH is released. They found that the increase in LH was most probably associated with the increase in adrenal progesterone, which should feed back negatively on the gonadotropins in the pituitary to reduce LH that accompanies the release of cortisol in response to stress. It was also discovered that progesterone can stimulate LH secretion by acting directly on the pituitary (Couzinet, et al. 1992). Because of the stimulation of the LH secretion, this may provoke a premature LH surge and thereby interfere with proper follicular maturation and ovulation. Furthermore, elevated LH concentrations at different stages of the menstrual cycle may have conflicting effects on the maturing follicle and on the developing oocyte and may result in early pregnancy loss, due to the egg not implanting properly.

There are many studies and research articles that support the observation of a rise in the LH after stress. It was also found that one of the major causes of decreased fertility is the occurrence of premature LH surges. Although there are many research articles, there are only a few clinical studies in humans that support our observation of a rise in LH after stress. The Puder study suggested that one of the major causes of decreased fertility of unstimulated cycles is the occurrence of premature LH surges (Puder et al. 2000). These premature LH surges, are usually a response to stress. When there is a premature LH surge, the follicle may not be ready, and ovulation will not occur. Injecting endotoxin, a mild inflammatory stress into his subjects revealed that those who received the highest dose of endotoxin exhibited decreased LH levels. Generally, for an LH surge to happen, there needs to be a high estrogen environment. They found that, although the subjects may have been in a low estrogen state when the endotoxin was administered, it lead to a significant stimulation of the LH levels. Thus, according to the Puder study, stress can bring on ovulation, although it may not be at the right time of the cycle. Additionally, one of the

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potential negative effects of poorly timed increase in LH may be premature luteinization. It could thus be speculated that the main general mechanism by which stress affects ovulation is by causing an increase in LH, or premature LH surges.

### **The Impact of Stress on The Reproductive System as it is Exposed to Physical Stress**

One of the many types of stress that a person can be exposed to is physical stress, such as exercise. Over the past decade, women have become much more physically active. Physical stress affects 6-79% of females, with the severity varying on the different type of athletic activities. More specifically, the mechanism by which exercise-associated abnormalities of the reproductive system generally stem from disruption at the hypothalamic level (Warren, Perloth 2001). The amenorrheic abnormalities within the general female population and within the population of females that were involved in sports were studied and found that the percentage with amenorrheic dysfunction was substantially higher in females that engaged in athletic activity (Constantini, Warren, 1994). The main mechanism by which stress affects the menstrual cycle and ovulation generally originates in the dysfunction of the hypothalamus and the disturbance of the GnRH pulse generator. However, the specific mechanisms are different based on the different type of athletic discipline. The percentage with irregularities varied with different types of sports or exercises. Additionally, experiments showed that exercise coupled with caloric restrictions severely affected the LH suppression, which negatively affected ovulation. However, the experiment also showed that exercise alone did not affect the LH rhythm (Loucks, 2000). The mechanism by which exercise, and the caloric restrictions affected the menstrual cycle and ovulation, was through the hormone, Leptin. The hormone leptin is a protein product of the obesity gene, and is an independent regulator of metabolic rate, and may be found to be a significant mediator of reproductive function. Multiple studies have shown that menstruation does not occur in women with low leptin levels, and thus they are unable to ovulate. (Laughlin & Yen 1997). However, these studies just prove to us how exercise coupled with unhealthy eating affects the LH rhythm. But how does exercise alone affect ovulation?

### **The B-endorphins and Catecholamines Effects**

Generally, when women exercise, it has been shown that there is an increase in the levels of B-endorphins and catecholamines. When there are increased levels of B-endorphins and catechol estrogens, studies have shown that the body responds with decreased levels of luteinizing hormone. However, Catecholamines have been found to regulate the luteinizing hormone (Russell et al, 1984). When Russell et al studied regularly menstruating active members of a swim club, he found the following results consistent with the above-mentioned mechanisms. They found that the swimmers that were most active, had higher estrogen

levels. They had an increase in their catecholamines, and specifically in their levels of norepinephrine, which plays a role in the hypothalamus to regulate hormone release. When there are high levels of norepinephrine, the release of LH was significantly increased. Thus, the increased release of LH in these athletes disrupted many of their menstrual cycles and caused delayed ovulation or anovulation (Russell et al., 1984).

The B-endorphin hypothesis was also confirmed in this study, where they found a rapid rise in plasma B-endorphins and B-lipotropins in competitively training athletes. As it was mentioned previously, B-endorphins cause a decrease in the luteinizing hormone. Additionally, the catecholamine increase that the athletes experienced, inhibited the breakdown of B-endorphins by blocking the enzyme that is needed to break it down. B-endorphin was shown to block ovulation through the mechanism of morphine sulfate. Pang et al 1977 showed that morphine suppresses the preovulatory release of luteinizing hormone, thus it blocked ovulation from occurring. However, they also discovered that naloxone hydrochloride which is the opiate antagonist, reverses the effect. Additionally, this can also be seen by the fact that if women are chronically exposed to heroin or methadone, they had a decrease in their gonadotropin release and the complete absence of the luteal phase, and thus they did not ovulate.

Norepinephrine has a great influence on the LH release hormone in the hypothalamus. As mentioned above, catecholamines actually regulate the Luteinizing Hormone, and assure that it is released at the proper time and with the proper amounts. However, Russell et al. found in their study that the B-endorphins which are released by athletes, actually suppresses norepinephrine and it cannot have its usual influences on the LH release hormone from the hypothalamus. Additionally, in order for the LH hormone to be released from the hypothalamus, it needs to be promoted by naloxone, a synthetic drug, which blocks the B-endorphins. It needs to block the B-endorphins, because as it was mentioned before, the B-endorphins caused a decrease in the LH, and blocked ovulation. Naloxone was discovered to help with menstrual cycle and ovulation regulation, through an experiment with athletes. They found that when a single dose of naloxone was given to runners, they responded with a pulsatile LH surge. Thus, B-endorphin suppression of LH can be overcome by giving naloxone to athletes with excessive beta endorphins (Russell et al. 1984).

### **Intense Physical Activity and Ovulatory Dysfunction**

There was a high correlation that was found between women who experienced intense physical activity and ovulatory dysfunction. It was found, regarding heavy runners, that only 50% of runners ovulated during a test month compared with 83% of controls. Fortunately, it was also shown that the ovulatory

dysfunction was only at the time of the intense physical activity, and once there was a less intense exercise schedule, their regular ovulation schedule returned (Gudmundsdottir et al, 2009). In addition to the blockage of the LH surge by B-endorphin, there is a common mechanism of ovulatory dysfunction which is called Hypogonadotropic Hypogonadism. Hypogonadotropic Hypogonadism is characterized by the failure of the pituitary gland to produce LH and Fsh, which play the key role in ovulation. The most common cause of this is excessive exercise (Fairley, Taylor 2003). Thus, women who exercise excessively are likely to develop this dysfunction, and without the production of LH and FSH, ovulation will not be able to occur. Additionally, women who exercise excessively can develop amenorrhoea because of a physiological reduction in the hypothalamic production of the gonadotropin releasing hormone. GnRH is also an imperative factor in ovulation, and if there is not enough GnRH being produced in the body, normal ovulation will not occur. This is characterized by the fact that the GnRH hormone regulates the timing and secretion of LH and FSH. If there is not enough GnRH being produced, it cannot regulate these hormones, and thus there will be a disturbance in the normal ovulation mechanism.

### **Moderate Physical Activity and Ovulatory Dysfunction**

Furthermore, there was additional evidence found which revealed another mechanism of ovulatory dysfunction in healthy women. The study was done by examining a group of healthy, moderately exercising women. Before this study, it was thought that the effects of exercise at the level of the GnRH pulsator was due to the changes in LH Pulsatility (Loucks et al. 1989). They found that like LH, alterations in FSH secretion can also significantly impact ovarian function by altering folliculogenesis. Usually, there is an elevation of FSH during the luteal-follicular transition, then a decline usually happens after ovulation, during the late follicular and early luteal phases. This study found that the usual rise in FSH is blunted in exercising women that have a luteal phase deficiency. This was the first report of an abnormality in the monthly pattern of FSH excretion in women (DeSouza, Miller et al. 1998). Thus, the above study provides us with an additional mechanism of how ovulation is disrupted through exercise. The rise of FSH during the luteal-follicular transition is very important for the LH surge that comes shortly after. If there is no rise in FSH, there will not be enough LH produced, and ovulation will not occur.

It was also found in the study done by Souza, Miller et al. that there was a progressive suppression of estradiol excretion during the follicular phase. A delay in the estradiol excretion will probably follow a delay in the growth of the follicles, and thus a delay in follicular dominance and ovulation. The data in this study was very much consistent with the data in the previous

studies in this paper. It supports the concept that in exercising women, both the luteal phase progesterone excretion and early follicular phase estrogen excretion decrease proportionally (Souza, Miller et al. 1998).

On the contrary to what was found in the study done by Souza, a study done by Jurkowski et al 1981 found opposite results. They studied the effects of exercise on the reproductive hormones, and what exercise had an effect on in the various stages of the menstrual cycle and ovulation. They studied nine women, and they found in all the women that when there was an increase in the intensity of the exercise, it affected the response of both the estradiol and the progesterone. They found that intense exercise increased the estradiol during both the follicular and luteal phases, although Souza found the opposite. In the luteal phase the progesterone also was increased, however, in the follicular phase they were lower. The low levels of estrogen can be a cause of anovulation, and the high levels of estrogen can also affect ovulation; there needs to be the right amounts in order for ovulation to occur.

### **Sporadic Anovulation in Physical Activity**

Although there is adequate evidence and many studies done to prove that physical activity affects ovulation, not all studies seem to have the same results. In a research study done by Ahrens, et al 2014 other evidence was found. They studied 259 healthy premenopausal, regularly menstruating women. Their focus was to see the changes in their hormones as they were physically active as well as to see if they had sporadic anovulation. It was found in their study that the women with higher physical activity did have some sporadic anovulation, but nothing that was statistically significant. However, they did find that women that had a more moderate physical activity routine, instead of an intense physical activity routine, did have a lower risk of anovulation.

This study may not support or agree with all the previous studies, but that does not discredit the studies that have been done in the past. There may have been limitations on this study that led to inaccurate results, and thus there may have been sporadic anovulation that was overlooked. This could have been due to the fact that the study was done based on the hormones present in the women that was used to predict if there was anovulation. If the study was done with ultrasound technology this would have given us more accurate results. Therefore, although this study did not find a mechanism that ovulation was affected by physical activity; there is adequate evidence from previous articles that support the hypothesis that there are mechanisms by which ovulation is affected by physical activity.

### **The Impact of Stress on The Reproductive System as It Is Exposed to Emotional Stress**

There is another type of stress which can critically affect a person's body and hormones, and that is emotional stress. Anxiety

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is a type of stress that is characterized by feelings of worry, anxiety or fear, and in many cases, it can strongly interfere and disrupt a person's daily life. Not only does anxiety affect a person on levels which are obvious and can be seen, but it also can affect a person on a biological level. When a person is under stress and has anxiety, their hypothalamus releases Corticotropin Releasing Hormone (CRH) as a response to the stress that they are experiencing.

Many studies, including one by Chen proved that the Corticotropin releasing hormone inhibits GnRH secretion (Chen et al. 1992). Additionally, corticotropin releasing hormone is found in many female reproductive organs; the ovaries, endometrial glands, trophoblasts etc. One mechanism by which stress can affect ovulation was found in an experiment done on women in-vitro. In a study done by Calogero et al, they also found that CRH interfered with reproductive and ovarian function by suppressing the HPG axis to release GNRH and it affected the pulsatility of the release of LH. This mechanism was also found and is consistent with the study done by Loucks. However, Calogero also discovered that CRH interfered directly at the gonadal level. Calogero studied many female rats and found that CRH inhibits FSH stimulated estrogen production, by decreasing the sensitivity of the rats to FSH. It was also found that CRH exerts an inhibitory effect on the formation of steroids (Calogero et al. 1996). This finding suggests that ovarian CRH has anti-reproductive actions that might be related to earlier ovarian failure which was observed in women with high anxiety and stress. Through their experiments they hypothesized and proved that this was through CRH inhibiting the production of FSH, thus leading to anovulation. If there is not an adequate release of FSH, the follicles will not be able to grow, there won't be a high estrogen environment and thus there will not be a LH surge, which will lead to anovulation. Thus, CRH may also be the major cause of anovulatory, or ovulatory dysfunction.

### Three Levels Where Stress Can Influence Sexual Functions

It is known that stress-related hormones can influence sexual functions at all three levels of the HPG axis; in the brain which will inhibit GnRH secretion, in the pituitary to interfere with GnRH induced LH release, and in the gonads to alter the stimulatory effects of gonadotropins on sex steroid secretion (Rivier, Rivest 1991).

It was hypothesized that when CRF is released during stress, it causes the GnRH hormone to be disrupted because of the short distance between CRF and GnRH secreting neurons. This is believed to be the main mechanism where stress inhibited reproductive functions, because of the direct anatomical connections between CRF axon terminals and dendrites of GnRH secreting neurons (Maclusky, Neranth 1988). This hypothesis was confirmed when the injection of CRF into the brain ventricles

of rodents immediately inhibited GnRH secretion. Additionally, they received further confirmation when they injected a CRF antagonist into the ventricle of the rat brain and it reversed the inhibitory action of stress on LH secretion (Rivier, Rivest 1991).

### The Effects of Stress on GnRH

The primary mechanism in which CRF inhibits GnRH is yet to be discovered, however; there was another mechanism found where CRF inhibits GnRH. It was found that when CRF was infused into both sides of the medial pre-optic area of the hypothalamus, it significantly decreased the GnRH release and plasma LH levels in female rats. Although there seems to consistently be negative effects of stress on the reproductive functions, the mechanisms will depend on the duration and frequency of the stimulus. For example, prolonged stress will initially have the responses mentioned above, but it will consistently inhibit LH release and then eventually block ovulation all together by peripheral mechanisms like altering the responsiveness of the pituitary and gonadal systems.

Most studies that were done agree that a very common cause of stress induced anovulation is by the mechanism of reduced hypothalamic GnRH input, which is caused by stress. If there is a decline in the GnRH secretion, it will directly reduce the secretion of LH and FSH and could wholly or partially disrupt folliculogenesis (Bourga, Loucks 2001). Bourga and Loucks discovered that amenorrheic athletes had less luteal progesterone secretion, fewer LH pulses per day, and higher cortisol levels. Furthermore, they also found that amenorrheic athletes that were anovulatory had the fewest LH pulses in a day and the highest cortisol levels. However, most of the studies done focused on specific stressors and how they affected a women's cycle or ovulation. Not many studies were done on how real life, daily stress has on reproduction.

### Daily Stress and its Effects on Reproductive Hormones

A mechanism on how daily stress affects women was provided to us by a study done by Nepomensachy Et Al. 2004. In contrast to our prior evidence, Nepomensachy and his fellow researchers found an alternative mechanism by which stress affects the reproductive hormones. As we have seen in previous research articles, stress is believed to affect reproductive function through a reduction in gonadotropins, which leads to a reduction in gonadal steroids. This also involved the stress activation of the HPA axis triggering the release of corticotropin-releasing hormone. The increase in CRH negatively affects the GnRH pulsatility and the cortisol surge causes a reduction of sensitivity to GnRH, leading to a reduction in the release of Gonadotropins (River, Vale, 1990). Because of the reduction in gonadotropin levels, it altered the maturation of the follicle, which delayed or prevented ovulation, with many other effects on the reproductive

hormones. However, in another study by Xiao et al 2000, they showed a different mechanism. They showed that while many other studies showed that intense levels of inflammatory stress inhibited the secretion of LH in female monkeys, in their studies they found that inflammatory stress can actually promote LH secretion. This was an interesting phenomenon as the monkeys also showed a rise in progesterone, and a rise in LH. Usually, when there is a rise in progesterone, it usually inhibits the secretion of LH (Xiao et al 2000).

In the study done by nepomnaschy, a new mechanism was discovered. They did not discover that the inhibition of progesterone during the luteal phase was triggered by a reduction in the levels of follicular gonadotropins. Rather, their results showed that during the mid-luteal phase, elevated cortisol levels predicted low progesterone levels, however; during the follicular phase, higher cortisol levels were associated with higher, not lower, gonadotropin levels. However, whether the mechanism that stress effects by lowering the gonadotropin levels, or increasing the gonadotropin levels, still has detrimental effects on the ovulation and implantation process. Low progesterone levels may cause a degenerative endometrium, and even if normal ovulation does occur, there may be a problem with implantation (Nepomnaschy, et. al.,2004). In order for a normal, healthy pregnancy to occur, there needs to be a normal implantation, and it is critical for the progesterone levels to be balanced.

Although it may seem that different types of stress may have different effects, it has also been shown that people that are more sensitive to stress, will have different responses. In contrast to studies that were done on humans, there was a study done by Herod, Dettmar et al. on monkeys in order to see which specific type of stress produced the most effects on the reproductive dysfunction. In their experiment, they found that the Monkeys with high cortisol levels varied according to the specific physical locations the monkeys were in, and which type of stress they were exposed to. It was found with their monkeys that they did show elevated cortisol in response to mild psychosocial plus metabolic stress. Also, the stress sensitive monkeys showed much higher cortisol levels than non-stressed monkeys. This finding would support the hypothesis that individuals with stress-induced amenorrhea do not have elevated baseline cortisol levels, but they are rather more likely to experience stress and thus have a higher probability of having elevated stress-induced cortisol when studies are performed.

Additionally, we know and have proven that elevated CRH suppresses the hypothalamic-pituitary-gonadal axis. However, the findings in Herod's studies with monkeys do not rule out a role for CRH acting as a neurotransmitter rather than a neuroendocrine hormone in causing sensitivity of the reproductive axis to stress. Increased CRH gene expression may be acting in a non-neuroendocrine manner to regulate other neurotransmitter systems that mediate functions of the reproductive axis,

including norepinephrine, dopamine, serotonin,  $\gamma$ -aminobutyric acid, and glutamate. Stress Sensitive monkeys have suppressed physiological release of serotonin, fewer serotonergic cells, and low expression of a number of genes in the serotonin pathway. However, when they were treated with a selective serotonin reuptake inhibitor, it increased the ovarian steroid hormone secretion. Thus, it caused the other functions to start working properly. This study may have given us a new mechanism by which the ovulatory system can be disrupted, by inhibiting neurotransmitter secretion (Herod, et al 2011).

### Conclusion

The mechanisms by which stress negatively affects ovulation is an amazing phenomenon with many mechanisms still yet to be discovered. Whether it is because of a physiological stress or physical stress, there have been a various amount of mechanisms that have been discovered, with many of them mentioned in this paper. While many of the mechanisms involved a premature LH surge, an increase in LH, inhibition of GnRH, Inhibition of FSH or excessive FSH, there were a variety of mechanisms that led to each outcome. Of all the mechanisms, there was not one specific one that dominated the others. Different stress caused different biological responses to occur, yet they all led to menstrual or ovulatory dysfunction. This data is extremely important as knowing exactly which mechanism is responsible for the menstrual or ovulatory dysfunction is imperative for assessing proper treatment. A suggestion for future research would be to see if stress affects ovulation subtly without causing amenorrhea.

### References

- Ahrens, Katherine A. et al. "The Effect of Physical Activity across the Menstrual Cycle on Reproductive Function." *Annals of epidemiology* 24.2 (2014): 127–134. PMC. Web. 31 Jan. 2018.
- Biller, Beverly M. K., et al. "Abnormal Cortisol Secretion and Responses to Corticotropin-Releasing Hormone in Women with Hypothalamic Amenorrhea \* | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic." OUP Academic, Oxford University Press, 1 Feb. 1990,
- Calogero, A.E., Burrello, N., Negri-Cesi, P., Papale, L., Palumbo, M.A., Cianci, A., Sanfilippo, S., D'Agata, R., 1996. Effects of corticotropin-releasing hormone on ovarian estrogen production in vitro. *Endocrinology* 137, 4161–4166.
- Chen, M.D., O'Byrne, K.T., Chiappini, S.E., Hotchkiss, J., Knobil, E., 1992. Hypoglycemic "stress" and gonadotropin-releasing hormone pulse generator activity in the rhesus monkey: role of the ovary. *Neuroendocrinology* 56, 666–673.
- Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M & Dina C 1998 A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 392 398–401.

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- Constantini NW & Warren MP 1994 Specific problems of the female athlete. In *Clinical Rheumatology, Exercise and Rheumatic Disease*. Eds RS Parish & NE Lane. Philadelphia: Balliere-Tindall
- Couzinet, B, et al. "Progesterone Stimulates Luteinizing Hormone Secretion by Acting Directly on the Pituitary." *The Journal of Clinical Endocrinology and Metabolism*, U.S. National Library of Medicine, Feb. 1992.
- De Souza Mary, et al. "High Frequency of Luteal Phase Deficiency and Anovulation in Recreational Women Runners: Blunted Elevation in Follicle-Stimulating Hormone Observed during Luteal-Follicular Transition 1 | *The Journal of Clinical Endocrinology & Metabolism | Oxford Academic*." OUP Academic, Oxford University Press, 1 Dec. 1998
- DeSouza, M. J., Miller, B. E., Loucks, A. B., et al. (1998). High frequency of luteal phase deficiency and anovulation in recreational women runners: blunted elevation in follicle-stimulating hormone observed during lutealfollicular transition. *Journal of Clinical Endocrinology and Metabolism* 83, 4220–4232
- Fairley, D. H., & Taylor, A. (2003). Anovulation. *BMJ : British Medical Journal*, 327(7414), 546.
- Gudmundsdottir, S.L., W.D. Flanders, L.B. Augestad; Physical activity and fertility in women: the North-Trøndelag Health Study, *Human Reproduction*, Volume 24, Issue 12, 1 December 2009, Pages 3196–3204,
- Hawkins, Shannon M., and Martin M. Matzuk. "Menstrual Cycle: Basic Biology." *Annals of the New York Academy of Sciences* 1135 (2008): 10–18. PMC. Web. 31 Jan. 2018.
- Herod, S. M. et al. "Sensitivity to Stress-Induced Reproductive Dysfunction Is Associated with a Selective but Not a Generalized Increase in Activity of the Adrenal Axis." *American Journal of Physiology - Endocrinology and Metabolism* 300.1 (2011): E28–E36. PMC. Web. 31 Jan. 2018.
- Jurkowski JE, Jones NL, Walker C, Younglai EV, Sutton JR: Ovarian hormonal responses to exercise. *J Appl Physiol* 1978, 44:109-114
- Laughlin GA & Yen SSC 1997 Hypoleptinemia in women athletes: absence of a diurnal rhythm with amenorrhea. *Journal of Clinical Endocrinology and Metabolism* 82 318–321.
- Loucks, A B, et al. "Alterations in the Hypothalamic-Pituitary-Ovarian and the Hypothalamic-Pituitary-Adrenal Axes in Athletic Women." *The Journal of Clinical Endocrinology and Metabolism*, U.S. National Library of Medicine, Feb. 1989,
- Loucks AB 2000 Exercise training in the normal female. In *Sports Endocrinology*, pp 165–180. Eds MP Warren & NW Constantini. Totowa, NJ: Humana Press, Inc.
- MacLusky NJ, Naftolin F, Leranath C. Immunocytochemical evidence for direct synaptic connections between (CRF) and (GnRH). *1988; 439:391 -395.*
- Marcus, M. D., Loucks, T. L. and Berga, S. L. (2001). Psychological correlates of functional hypothalamic amenorrhea. *Fertility and Sterility* 76, 310–316.
- Mary Jane De Souza, B. E. Miller, A. B. Loucks, A. A. Luciano, L. S. Pescatello, C. G. Campbell, B. L. Lasley; High Frequency of Luteal Phase Deficiency and Anovulation in Recreational Women Runners: Blunted Elevation in Follicle-Stimulating Hormone Observed during Luteal-Follicular Transition, *The Journal of Clinical Endocrinology & Metabolism*, Volume 83, Issue 12, 1 December 1998
- Nepomnaschy, Pablo A.; Welch, Kathy; McConnell, Dan; Strassmann, Beverly I.; England, Barry G. (2004). "Stress and female reproductive function: A study of daily variations in cortisol, gonadotrophins, and gonadal steroids in a rural Mayan population." *American Journal of Human Biology* 16(5): 523-532.
- Pang CN, Zimmerman E, Sawyer CH: Morphine inhibition of the preovulatory surges of plasma LH and FSH in the rat. *Endocrinology* 101: 1726, 1977
- Puder, Jardena J., et al. "Stimulatory Effects of Stress on Gonadotropin Secretion in Estrogen-Treated Women 1 | *The Journal of Clinical Endocrinology & Metabolism | Oxford Academic*." OUP Academic, Oxford University Press, 1 June 2000.
- Rivier C, Rivest S: Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis peripheral and central mechanisms. *Biol Reprod* 1991, 45:523-532
- Rivier C, Vale W. 1990. Cytokines act within the brain to inhibit luteinizing hormone secretion and ovulation in the rat. *Endocrinology* 127:849–856
- Russell JB, Mitchell D, Collins DL, Musey PI, Collins DC: The relationship of exercise to anovulatory cycles in female athletes: hormonal and physical characteristics, *Obstet Gynecol* 1984; 63:452-456
- Warren, MP, and NE Perlroth. "The Effects of Intense Exercise on the Female Reproductive System." *Journal of Endocrinology*, 1 July 2001.
- Xiao E, Xia-Zhang L, Ferin M. 2002. Inadequate luteal function is the initial clinical cyclic defect in a 12-day stress model that includes a psychogenic component in the rhesus monkey. *J Clin Endocrinol Metab* 87: 2232–2237
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. *Nature* 372 425–432.