What is the mechanism of stress, and how does it affect reproduction?
--- "When pushed too far, subfertility occurs"

Here is an ad hoc selection of a few abstracts from my files on psychoneuroimmunoendocrinology papers addressing ovulation, reproduction (folliculogenesis).

The first few are representative of animal work, and then several abstracts represent the literature on stress in the human female. In between, let's display our cyclic profile data on a non-baseline menstrual cycle with delayed ovulation. This record illustrates how our Ovulona™ device can detect the effect of stress on the course of the menstrual cycle. Non-baseline refers to any real-life female with all the stressors of our daily life, no baseline simplifications of conditions such as we need to try and approach what we would call ideality (at least in physical science we would…).

Should these abstracts turn out to be too stressful, then you may perhaps enjoy better another selection I just came across, Introduction to psychoneuroendocrinology volume: is there a neurobiology of love? http://cogweb.ucla.edu/Abstracts/NeuroLove_98.html

---

J Physiol. 1977 Mar;266(1):13P-14P. Related Articles, Links

A ventral tract from the bed nucleus of the stria terminalis to the amygdaloid complex in the monkey (Macaca fascicularis): possible pathway in the regulation of ovulation [proceedings].

Novotny GE.

PIP: Characteristics of a ventral tract from the bed nucleus of the stria terminalis **(BST)** to the amygdaloid complex in the monkey (Macaca fascicularis) are described. A system of approximately 200 fiber bundles lying between the BST and baso-lateral part of the amygdaloid complex was identified and postulated to be monosynaptic. The bundles consist of unmyelinated fibers with a median diameter of .16-.20 mcm. No axons could be found with a diameter greater than .55 mcm, and 8% of the fibers had a diameter of less than .10 mcm. The total number of axons in the tract was calculated to be 500,000. It is concluded that the direction of conduction in this pathway is from BST to the amygdala, and, since the neurones of BST contain estradiol, that **this tract may be involved in the regulation of ovulation.**

C R Seances Soc Biol Fil. 1979;173(1):1326. Related Articles, Links

[New data on serotoninergic mechanisms in ovulation in the cyclic female rat]

[Article in French]

Satli MA.

Injection of parachlorophenylalanine on dioestrus II at 18:00 was shown to decrease ovulation frequency in 4-day cyclic female rats. This effect was overcome by either HTP,

83 Davis Ranch Road, P.O. Box 122, Bellvue, Colorado 80512, USA
Vaclav Kirsner, Ph.D., Chairman and CEO
vaclavkirsner@yahoo.com
970-484-1272

or oestradiol benzoate, when administered on dioestrus II, at 18:00 and 10:00 - 11:00 respectively. No antiovulatory action of PCPA was observed on prooestrus at 13:00. **These results provide support to the specificity of action of serotonin in the control of ovulation in the cyclic rat. They also suggest an interaction of serotonin and oestrogens in this control.**

Anim Reprod Sci. 2000 Jul 2;60-61:743-52. Related Articles, Links

What is stress, and how does it affect reproduction?

Dobson H, Smith RF.
Department of Veterinary Clinical Science and Animal Husbandry, University of Liverpool, Leahurst, Wirral, Neston, UK.

Stress is revealed by the inability of an animal to cope with its environment, a phenomenon that is often reflected in a failure to achieve genetic potential. Field data from dairy cows show that stressors such as milk fever or lameness increase the calving to conception interval by 13-14 days, and an extra 0.5 inseminations are required per conception. We suggest that **a variety of endocrine regulatory points exist whereby stress limits the efficiency of reproduction.**

Transport produces an immediate constant increase in arginine vasopressin (AVP) and corticotrophin-releasing hormone (CRH) secretion in ewes, but adrenocorticotrophic hormone (ACTH) reaches a maximum in the first hour while cortisol is highest during the second hour. In contrast, after an insulin injection, the hypothalamo-pituitary-adrenal (HPA) response is delayed occurring only after glucose decreases below a threshold. Changes in AVP, CRH and ACTH each follow a similar time course, but eventually the secretion of AVP and CRH decreases while glucose is still at a nadir. Negative feedback effects appear to operate mainly at the pituitary level during transport but at the hypothalamus during hypoglycaemia.

We also have endocrine evidence to show that **stressors interfere with precise timings of reproductive hormone release within the follicular phase**. Transport, or insulin, reduce the frequency and amplitude of gonadotrophin-releasing hormone and LH pulses, suggesting that these stressors exert effects at the hypothalamus or higher centres in the brain. Both stressors also delay the onset of the luteinising hormone (LH) surge.

Preliminary results suggest that **opioids mediate these effects** but progesterone/glucocorticoid receptors are not involved because the antagonist, RU486, is unable to reverse insulin-induced delays in the LH surge. There is also evidence to support effects at pituitary level because exogenous ACTH, or transport, reduce the amount of LH released by challenges with GnRH. The reduction in endogenous GnRH/LH secretion ultimately deprives the ovarian follicle of adequate gonadotrophin support leading to reduced oestradiol production by slower growing follicles.

Thus, there is **a level of interference by stressors at the ovary**.

Reproduction is such an important physiological system that animals have to ensure that they can respond to their surroundings; thus, it is advantageous to have several protein mechanisms, i.e. at higher brain, hypothalamus, pituitary and target gland levels.

However, when pushed too far, subfertility occurs.
Publication Types: Review, Tutorial **Author Keywords:** Stress; Reproduction; Subfertility

---

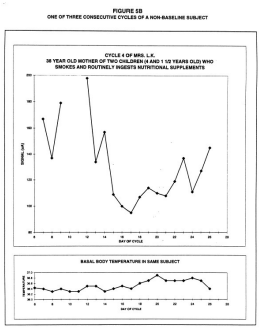
Ann N Y Acad Sci. 1993 Oct 29;697:106-16. Related Articles, Links

Neuropeptides, the stress response, and the hypothalamo-pituitary-gonadal axis in the female rhesus monkey.
Ferin M.
Center for Reproductive Sciences, College of Physicians and Surgeons, Columbia University, New York, New York 10032.
In conclusion, we have demonstrated that in the primate increased activity of the immune system and the consequent IL-1 release result in the activation of neuropeptides of the adrenal axis, mainly CRF and AVP. These neuropeptides, through a direct effect on the GnRH pulse generator or indirectly through the hypothalamic endogenous opioid peptides, **inhibit the GnRH pulse generator**. Some of the POMC derivatives, such as alpha-MSH, may antagonize these effects.
The consequential decrease in GnRH pulse frequency results in an **acute decrease in LH and FSH secretion**. **This decrease in gonadotropin release may explain the deleterious effects of stress on the menstrual cycle. However, an acute decrease in gonadotropins following activation of the adrenal axis is not observed in the presence of estradiol.**
Thus, during the menstrual cycle, a relative protection against the deleterious effects of acute stress may exist. How potent this protective mechanism is against repetitive stress is not known.
Publication Types: Review, Tutorial

Ann Med. 1997 Jun;29(3):215-9. Related Articles, Links

Stress-related disturbances of the menstrual cycle.
Xiao E, Ferin M.
Department of Obstetrics and Gynecology and Center for Reproductive Sciences, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA.
Stress is a common cause of hypothalamic amenorrhoea. In our laboratory, we have studied the effects of an inflammatory-like stress on gonadotropin secretion and on the menstrual cycle in a nonhuman primate model. In this short review, we summarize some of our findings regarding the mechanisms whereby stress induces disturbances of reproductive function.
Our data indicate that the **hypothalamic-pituitary-adrenal axis, through the release of corticotropin-releasing hormone and vasopressin, plays a mediatory role**. One type of action is exerted through a central process resulting in the inhibition of the gonadotropin-releasing hormone pulse generator. The other type is mediated by a peripheral pathway stimulatory to gonadotropin secretion. Activation of one or the other

pathway is determined by the ovarian endocrine milieu. Both actions presumably result in deleterious effects on the menstrual cycle.
Publication Types: Review, Tutorial



"Non-baseline cycle with delayed ovulati

jpeg in IrfanView [For the Alphabet]

…stressors interfere with precise timings…

Int J Fertil. 1990 Jan-Feb;35(1):8-13. Related Articles, Links

The role of stress in female reproduction: animal and human considerations.
Chatterton RT.
Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, Illinois.
Stress, of both physical and emotional origin, has effects on the reproductive system. Although both ACTH and glucocorticoids are elevated in stress, there is little evidence that these hormones directly affect gonadotropin secretion or ovulation. Corticotropin-releasing factor (CRF) does interact with gonadotropin-releasing hormone (GnRH)-producing neurons, probably through an opioidergic pathway, suppressing gonadotropin secretion. Opioids, primarily beta-endorphin, originating through CRF-independent mechanisms in the brain or even the pituitary may also inhibit GnRH production. **Tonic, pulsatile gonadotropin secretion is inhibited by stress and by administered morphine, but morphine does not block the estrogen-induced preovulatory surge in primates.** Accordingly, **impaired follicular development appears to be the most common cause of reproductive dysfunction** attributable to stress in the human female.
New developments in the understanding of the role of stress in reproduction must take into consideration the many differences between the hormonal responses to stress in the human and laboratory animals.
Publication Types: Review, Tutorial

Ann N Y Acad Sci. 1997 Jun 17;816:9-21. Related Articles, Links

Development of the hypothalamic-pituitary-ovarian axis.
Apter D.
Department of Obstetrics & Gynecology, Helsinki University, Finland.
The onset of puberty is a centrally driven process, the detailed mechanisms of which are not known. It is translated into an increased activity of the hypothalamic GnRH pulse generator. This in turn is seen as increased pituitary pulsatile secretion of LH and FSH. LH pulses are observed even in midchildhood, particularly after the onset of sleep. **Onset of puberty is associated with a greater increase in LH pulse amplitude than frequency** and a much greater increase in LH and FSH. A progressive increase in daytime pulsatility occurs, with a gradual reduction of sleep-entrained amplification. Prepubertal FSH concentrations are relatively high in girls, and continous ovarian follicular growth and atresia take place, with estradiol concentrations being higher than in boys.
Only after the steep early pubertal increase in LH, ovarian steroidogenesis is activated, with increases in androgen and estrogen secretion. Under further FSH stimulation, follicular growth and maturation proceed. The first menstrual cycles are mostly anovulatory for 1 to 2 years. Luteal phase insufficiency is common the first five years after menarche.
Publication Types: Review

Ther Umsch. 2002 Apr;59(4):175-81. Related Articles, Links

[Influence of the ovarian cycle on the central nervous system] [Article in German]
Kuhl H.
Zentrum der Frauenheilkunde und Geburtshilfe Klinikum der J.W. Goethe-Universitat Frankfurt. H.Kuhl@em.uni-frankfurt.de
Estradiol, progesterone and some of their metabolites modulate the activity of neurotransmitters and neuropeptides in the CNS. The distribution and concentrations of sex steroids in the various CNS regions is partly dependent on the serum levels, but also on the local synthesis of the steroids. **In general, estradiol and testosterone exert a stimulatory, progesterone an inhibitory effect on neuronal activities which are mediated by excitatory (e.g. glutamate, aspartate), and inhibitory amino acids (e.g. GABA) and neuropeptides (e.g. beta-endorphin), respectively.**
Gonadotropin release is primarily governed by the rhythm of pulsatile secretion of GnRH in the hypothalamus which is controlled by estradiol and progesterone by means of inhibitory or stimulatory modulation of the amplitude and frequency of GnRH pulses. The discharges of GnRH neurons triggered by excitatory amino acids are modulated by estradiol, while the inhibitory effect of progesterone is mediated by GABA and beta-endorphin which cause hyperpolarization of the GnRH neurons and consequently a reduced pulse frequency.
The pulse amplitudes are primarily influenced by estradiol, but neuropeptide Y, neurotensin and noradrenaline contribute to their preovulatory enhancement. The postovulatory rise in core temperature is caused by the increasing level of progesterone and its metabolite 3 alpha-pregnanolone, respectively. **Despite of this, up to 20% of**

ovulatory cycles do not show any rise in body temperature. Although 3 alpha-pregnanolone has sedative activities, there is no change in sleep quality during the luteal phase due to their low serum levels.
It could be demonstrated that performance on tests of articulatory and fine motor skills are enhanced in the late follicular phase as compared to the menstruation phase, while spatial ability was better during menses. Estrogens may influence mood and well-being in a favorable manner, while in predisposed women progesterone may cause symptoms of premenstrual syndrome. In most women there are, however, no cycle-dependent mood changes. An increase in appetite can be observed during the periovulatory phase and before menses, while sexual interest increases in the follicular phase. **Somatic complaints (back pain, abdominal pain, breast tenderness) which are highest before and during menstruation, are probably associated with a lowered pain threshold due to a fall in the beta-endorphin levels in the CNS.**

Indian J Physiol Pharmacol. 2001 Oct; 45(4):395-407.

Related Articles, Links

Hypothalamo-pituitary-gonadal axis in control of female reproductive cycle.
Tandon OP, Chintala R.
Department of Physiology, University College of Medical Sciences & GTB Hospital, Shahdara, Delhi-110 095.
Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus is pivotal to the regulation of reproductive physiology in vertebrates. The characteristic periodic secretion of gonadotropin releasing hormone (GnRH) from the medial basal hypothalamus (MBH), at the rate of one pulse an hour is essential for the maintenance of the menstrual cycle. These pulses are due to oscillations in the electrical activity of the GnRH pulse generator in the MBH.
The GnRH pulse generator is under the influence of an assortment of interactions of multiple neural, hormonal and environmental inputs to the hypothalamus. Hence, a number of conditions such as stress, drug intake, exercise, sleep affect the activity of this pulse generator.
Any deviation of normal frequency results in disruption of normal cycle. The cycle can become anovulatory in the hypothalamic lesions and can be restored by exogenous administration of pulsatile GnRH. Of late, studies have shown that pulse generator activity is also maintained by specific metabolic signals meant for energy homeostasis. Studies are in progress to work out cellular basis of GnRH pulse generator's rhythmic activation and role of Ca++ as second messenger for GnRH stimulated gonadotropin release. New concepts are emerging to find the existence of an FSH releasing factor, which independently regulates the activity of FSH.
Publication Types: Review