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شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



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**PARAMETERS AFFECTING LUTEAL
PHASE LENGTH IN REGULARLY
OVULATING WOMEN**

14420

Thesis

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Introduction



INTRODUCTION

Menstruation is the monthly loss of blood from the uterus but precisely it is the monthly bleeding from a secretory endometrium; the latter is a better definition, as pseudo menstruation may occur at monthly intervals from a proliferative anovular endometrium. The endometrium, after ovulation, is prepared into a progestational type suitable for the implantation of a fertilized ovum; if there had been no fertile intercourse, menstruation occurs from this secretory endometrium. That is why menstruation has been called "the tears of disappointed endometrium". Menstruation is particular to human beings and other primates and is absent in almost all other animals.⁽¹⁾

Ovarian cycle

To understand the normal menstrual cycle, it is helpful to divide the cycle into 3 phases, the follicular phase, ovulation and the luteal phase.

The follicular phase:

During the follicular phase an orderly sequence of events takes place which ensure that the proper number of follicles is ready for ovulation. In the human ovary the end result of this follicular development is (usually) one surviving mature follicle. This process, which occurs over the space of 10 – 14 days, features a series of sequential actions of hormones and autocrine/paracrine peptides on the follicle, leading the follicle destined to ovulate through a period of initial growth from a primordial follicle through the stages of the pre antral, antral and pre ovulatory follicle.⁽²⁾

Events in the preantral follicle:

There is initial follicular growth occurs independently of hormone influence, FSH stimulation propels follicle to the preantral stage, followed by FSH induced aromatization of androgen in the granulosa results in the production of estrogen and together, FSH and estrogen increase the FSH receptor content of follicle.^(3,4)

While in the antral follicle: The follicular phase estrogen production is explained by the two cell, two gonadotropin mechanism.⁽⁵⁾ and selection of the dominant follicle is established during days 5 – 7, and consequently, peripheral levels of estradiol begin to rise significantly by cycle day 7.⁽⁶⁾ The estradiol levels, derived from the dominant follicle, increase steadily, and through negative feedback effects, exert a progressively greater suppressive influence on FSH release. Then, the mid follicular rise in estradiol exerts a positive feedback influence on LH secretion. This LH levels rise steadily during the late follicular phase, stimulating androgen production in the theca.^(7,8)

The follicular response to the gonadotropin is modulated by a variety of growth factors and autocrine/paracrine peptides. Also inhibin and less importantly follistatin secreted by the granulosa cells in response to FSH, directly suppresses pituitary FSH secretion. While the activin, originating in both granulosa and pituitary, augments FSH secretion and action.⁽⁹⁾

In the preovulatory follicle. The estrogen production becomes sufficient to achieve and maintain peripheral threshold concentration of estradiol that are required to induce LH surge. Which acting through its receptors, LH initiates luteinization and progesterone production in the granulosa layer. This preovulatory rise in progesterone facilitates the

positive feedback action of estrogen and may be required to induce the mid cycle FSH peak.⁽¹⁰⁾

Ovulation:

The preovulatory follicle through the elaboration of estradiol, provides its own ovulatory stimulus. Considerable variation in timing exists from cycle to cycle, even in the same woman. A reasonable and accurate estimate places ovulation approximately 10 – 12 hours after the LH peak and 24 – 36 hours after peak estradiol levels are attained.^(11,12) The onset of the LH surge appears to be the most reliable indicator of impending ovulation, occurring 34 – 36 hours prior to follicle rupture.⁽¹³⁾ A threshold of LH concentration must be maintained for 14 – 27 hours in order for full maturation of the oocyte to occur. Usually LH surge lasts 48 – 50 hours.^(13,14)

The ovulatory events:

The LH surge stimulates resumption of reduction division in the oocyte, luteinization of the granulosa, and synthesis of progesterone and prostaglandins within the follicle. The progesterone enhances the activity of proteolytic enzymes responsible together with prostaglandins, for digestion and rupture of the follicular wall. Also progesterone influenced mid cycle rise in FSH serves to free the oocyte follicular attachments, to convert plasminogen to the proteolytic enzyme, plasmin, and to ensure that sufficient LH receptors are present to allow an adequate normal luteal phase.^(15,16)

Luteal phase:

Before rupture of the follicle and release of the ovum, the granulosa cells begin to increase in size and assume a characteristic vacuolated appearance associated with the accumulation of a yellow pigment, lutein, which lends its name to the process of luteinization and the anatomical subunit, the corpus luteum. During the first 3 days after ovulation, the granulosa cells continue to enlarge. In addition, theca lutein cells may differentiate from the surrounding theca and stroma to become part of the corpus luteum.⁽¹⁷⁾ Capillaries penetrate into the granulosa layer (under the influence of factors that induce angiogenesis and mitogenesis that may include fibroblast growth factors, platelet derived growth factor, insulin like factor, heparin binding growth factor and vascular endothelial growth factor), reach the central cavity, and often fill it with blood. By day 8 or 9 after ovulation, a peak of vascularization reached, associated with peak levels of progesterone and estradiol in the blood.^(18 - 23)

The endometrial cycle:

The sequence of endometrial changes associated with an ovulatory cycle has been carefully studied by Noyes in the human. From these data a description of menstrual physiology has developed based upon specific anatomic and functional changes within glandular, vascular and stromal components of the endometrium.⁽²⁴⁾ The changes will be discussed in five phases:

- (1) The menstrual endometrium.
- (2) The proliferative phase.

- (3) The secretory phase.
- (4) Preparation for implantation.
- (5) Finally the phase of endometrial break down.

The endometrium can be divided morphologically into an upper two-thirds "functionalis" layer and a lower one-third "basalis" layer. The purpose of the functionalis layer is to prepare for the implantation of the blastocyst and, therefore, it is the site of proliferation, secretion, and degeneration. The purpose of the basalis layer is to provide the regenerative endometrium following menstrual loss of the functionalis.⁽²⁵⁾

The menstrual endometrium:

The menstrual endometrium is a relatively thin, but dense tissue. It is composed of the stable, non functioning basalis component and a variable, but small, amount of residual stratum spongiosum.

The proliferative phase:

The proliferative phase is associated with ovarian follicle growth and increased estrogen secretion, undoubtedly as a result of this steroidal action, reconstruction and growth of the endometrium are achieved. The glands are most notable in this response. At first they are narrow and tubular, lined by low columnar epithelium cells. Mitoses become prominent and pseudostratification is observed. During proliferation, the endometrium growth from approximately 0.5 mm to 3.5 – 5.0 mm in height. This proliferation is mainly in the functionalis layer. Restoration of tissue constituents has been achieved by estrogen-induced new growth as well as incorporation of ions, water, and amino acids. The stromal ground substance has reexpanded from its menstrual collapse. Although

true tissue growth has occurred, a major element in achievement of endometrial height is "re inflation" of the stroma.

A major feature of this estrogen dominant phase of endometrial growth is the increase in ciliated and microvillous cells. Ciliogenesis begins on days 7 - 8 of the cycle. This response to estrogen is exaggerated in hyperplastic endometrium that is the result of hyperestrogenism.⁽²⁶⁾

The secretory phase:

After ovulation, the endometrium now demonstrates a combined reaction to estrogen and progesterone activity. Most impressive is that total endometrial height is fixed at roughly its pre ovulatory extent (5 - 6 mm) despite continued availability of estrogen. This restraint or inhibition is believed to be induced by progesterone. This limitation of growth is associated with a decline in mitosis and DNA synthesis, significantly due to progesterone interference with estrogen receptor expression and progesterone stimulation of 17B - hydroxy steroid dehydrogenase and sulfotransferase which convert estradiol to estrone sulfate (which is rapidly excreted from the cell. The secretory events within the glandular cells, with progression of vacuoles from intracellular to intraluminal appearance, are well-known and take place approximately over a 7 days post ovulatory interval. At the conclusion of these events the glands appear exhausted, the tortuous lumina variably distended, and individual cell surfaces fragmented and lost (saw tooth appearance). Stroma is increasingly edematous and spiral vessels are prominent and densely coiled.⁽²⁷⁾