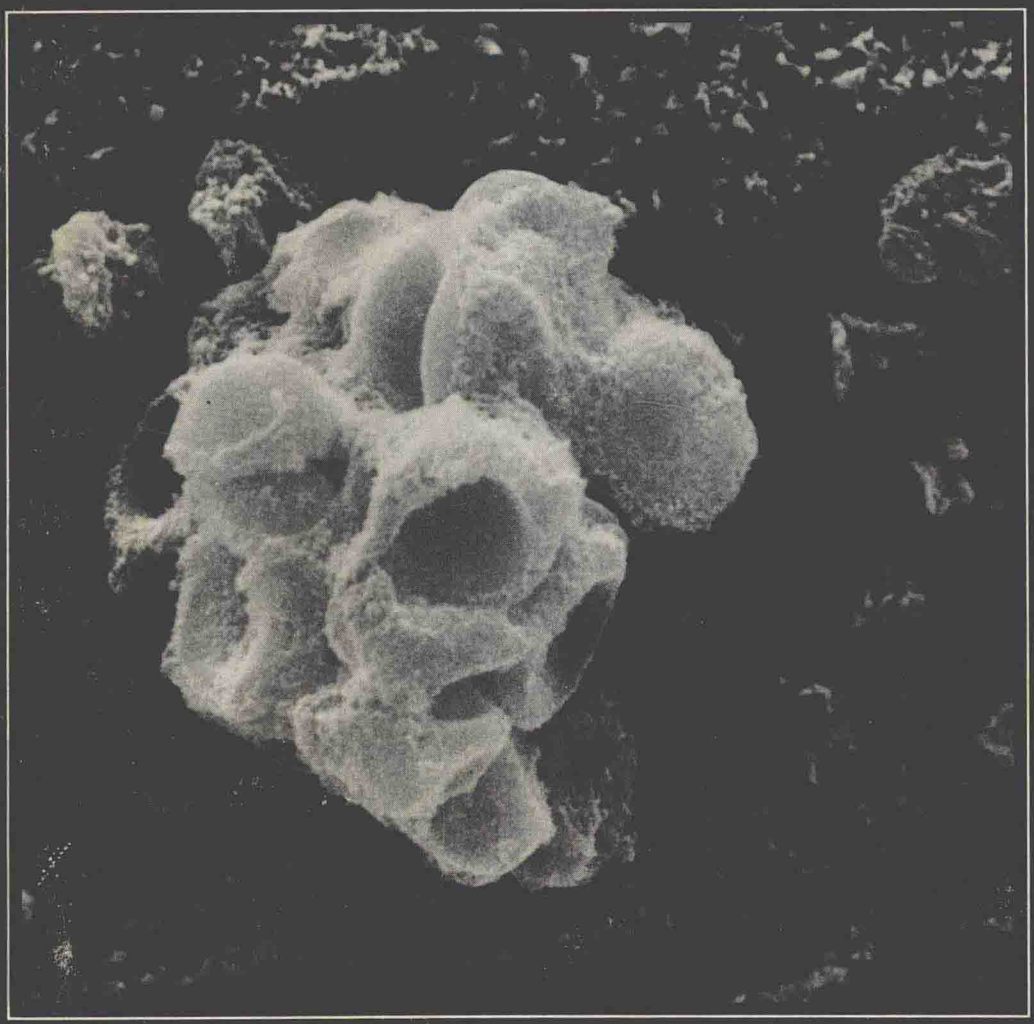
# THE ENDOMETRIUM

## Hormonal Impacts



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# THE ENDOMETRIUM

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# PREFACE

Although the physiology of the menstrual cycle appears clear and easily explained by a balance in the concentration of various sex steroid hormones, numerous details of its mechanism are still poorly understood and little is known about the relationship among clinical events, plasma hormone concentrations, molecular impacts on target tissues and their regulation. In the following chapters, the authors have attempted to establish a correlation between endometrial histology and well-understood physiologic events of the menstrual cycle. They have provided up-to-date information on the effects of various hormones and combinations of hormones on the endometrium. The interdependence of endometrial morphology, molecular biology, endocrinology and physiology, provides grounds for a better understanding of the complex mechanism of the menstrual cycle, and sheds some light on its pathophysiology. Such an approach adds another dimension to interpretation of many menstrual abnormalities and numerous aspects of infertility in women with normal physiognomies and apparently regular menstrual cycles.

The pathologist must be aware of these new concepts since a knowledge of functional changes reflected in hormone serum levels and sex steroid receptor concentrations allows a more detailed analysis and a better interpretation of the structural features of the endometrium. This information placed in the proper clinical context can help the gynecologist provide optimal therapy. The reader will find a valuable reference for a synthesis of clinical, morphological, and biochemical data related to the menstrual cycle and its aberrations.

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# MENSTRUAL CYCLE: SOME UNCERTAIN ASPECTS

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## INTRODUCTION

For a long time endometrial biopsy was the only unbiased and precise parameter for clinical investigation of the human menstrual cycle. With the development of techniques to measure hormone concentrations in plasma, the earlier methodology was abandoned. Interest in this target tissue is again growing, but for different reasons. Because hormonal measurements indicate a momentary physiological value, whereas the endometrium reflects various stages of hormonal influence, sampling and histological examination of this tissue can demonstrate the normal correlated influences of hypophysial and ovarian hormones, or show a functional disorder of the hypothalamic-ovarian axis. New insights into the cellular and molecular physiology of the endometrium are probably necessary for understanding implantation mechanisms. This paper will be devoted to the effects of hormones on the endometrium. Rather than a sempiternal report on the known physiological aspects of the menstrual cycle, we will focus on the unknown aspects of synchronized events that control human reproduction. It does not seem useful to describe the concentrations of the different hypophysial and ovarian hormones or necessary to relate the feedback system or the hormonal mode of action at the cellular level. Instead we will attempt to describe the controversial aspects of menstrual cycle regulation, and to examine specific and still unclear points of this regulation.

## CENTRAL LEVEL

### Hypophysial Activity and Sensitivity

Control of the menstrual cycle is much more complex than the classic and well demonstrated estrogen-induced feedback mechanism (Bogdanove, 1963; Knobil, 1974). Two phenomena are most important for control of the cycle in primates. The first is the variable hypophysial sensitivity to luteinizing hormone releasing hormone (LHRH) during the cycle; administration of repetitive doses of LHRH (10 µg at 2-hour intervals, 5 successive times) during the menstrual cycle produces profound changes in pituitary response, in concert with cyclic ovarian steroid levels (Wang et al., 1976). During the late follicular phase, subsequent responses to successive LHRH doses are greater. The LH response is maximal during the preovulatory period, whereas gonadotropin rises show a progressive decrease after injection of LHRH. The LH response then decreases during the luteal phase (Yen and Lein, 1976). These variations in hypophysis responsiveness are clearly dependent on circulating estrogen (Yen and Tsai, 1972; Jaffe and Keye, 1974; Young and Jaffe, 1976). The second phenomenon is the autonomy of the mediobasal hypothalamus, which is not dependent on a signal from the preoptic area for induction of the preovulatory LH peak (Krey et al., 1975). Thus, it is not surprising that no LHRH surge could be detected before or during the preovulatory LH peak (Barraclough, 1979). With this experimental and clinical background, we wanted to examine how the preovulatory LH peak is determined in primates.

Yen et al. (1972) have suggested that there are two pools of pituitary gonadotropins. One would be readily releasable and discharged in response to a brief small pulse of LHRH. Indeed, changing pituitary responses to pulses of different amounts of LHRH (10 to 300 µg) demonstrate that the pituitary can detect relatively small variations in circulating LHRH. A second reserve pool would then be activated and released after a more prolonged LHRH stimulation. This pool would be dependent on the level and duration of estradiol secretion (Yen et al., 1972; Wang et al., 1976; Hoff et al., 1977).

Based on these studies, a hypothesis integrating the total regulation of the menstrual cycle can be postulated. The sensitivity of the hypophysis would be enhanced by the rhythm of estradiol secretion, i.e., the higher the estradiol level, the more important gonadotropin release. Hypothalamic LHRH secretion would be essential in that it would have a permissive, but obligatory role (Yen, 1978). In this context the ovary would be the real timer regulating this complex system. This hypothesis is perhaps oversimplified; however, recently the essential permissive role of LHRH pulses has been

demonstrated (Knobil, 1980a,b). Female rhesus monkeys were subjected to bilateral irradiation, producing lesions in the arcuate region of the mediobasal hypothalamus and suppressing gonadotropin-releasing hormone (GnRH) production. This resulted in the reduction of LH, FSH and estrogen and in cessation of the menstrual cycle. Hormonal secretions and the menstrual cycle resumed upon administration of pulses of GnRH on an hourly regimen (Knobil et al., 1980). A similar GnRH infusion regimen induced normal ovulatory-menstrual cycles in prepubertal female rhesus monkeys; when infusions were discontinued, the animals promptly reverted to their prepubertal state (Wildt et al., 1980).

These experimental data have had few but interesting clinical applications (Crowley and McArthur, 1980; Hanker and Schneider, 1980; Layendecker et al., 1980). A few cases of hypothalamic amenorrhea have been at least temporarily corrected by hourly pulsatile LHRH administration, and two pregnancies resulted.

Previous attempts to modify hypophysis sensitivity or to stimulate gonadotropin secretion have been disappointing. Administration of estradiol or synthetic estrogen (ethinyloestradiol, moxestrol) during the follicular phase usually delays ovulation and subsequently shortens the luteal phase (Carguille et al., 1973; Gautray et al., 1977). Administation of LHRH and potent analogs (at various doses) has not improved ovulatory disorders. LHRH pulsatile infusion, although difficult, may be very promising clinically. It demonstrates the permissive role of LHRH secretion; however, the origin of this hypothalamic activity remains unknown.

## Role of Prolactin

The role of prolactin (PRL) in primate reproduction is not well understood. Variations in plasma PRL levels during the menstrual cycle are controversial (McNeilly and Chard, 1976; Gautray et al., 1977; Vekemans et al., 1977); however there is no evidence of a consistent change in PRL during the menstrual cycle. Whether PRL is necessary for maturation of the ovarian follicle is unknown, although hyperprolactinemia, either "dysfunctional" or due to pituitary adenoma (Boyd and Richlin, 1978) can induce (or be associated with) different menstrual cycle disorders from amenorrhea to luteal insufficiency (Corenblum et al., 1976; Seppala et al., 1976; Muhlenstadt et al., 1978; Del Pozo et al., 1979). The mechanism of hyperprolactinemia without clinically demonstrable pituitary adenoma is difficult to ascertain, but may be of hypothalamic origin or related to a specific disorder of the PRL-producing cells. There is no means to distinguish between neural or cellular disorders, and to date, pharmacological tests have been unreliable (Genazzani et al., 1980).

## Role of Neurotransmitters

Results of studies on rodents support the hypothesis that amines and neuropeptides are involved in the control of pituitary hormone secretion (Boyd and Reichlin, 1978; Fuxe et al., 1978; Meites et al., 1979). The best known brain modulation (by monoaminergic mechanisms) concerns dopamine (DA) and PRL (Boyd and Reichlin, 1978). Morphological studies have demonstrated that DA, norepinephrine (NE) and LHRH receptors are concentrated in the median eminence, where these substances are present in high concentrations. This supports the hypothesis of a possible interaction between DA, NE and LHRH receptors and a possible monoaminergic control of gonadotropin secretion.

In the rat, a decreased DA turnover, a sharp increase in NE turnover during the afternoon of proestrus (Ben-Jonathan et al., 1977) and a significant increase in NE concentration between the morning and afternoon of proestrus in hypothalamic nuclei (Selmanoff et al., 1977) have been demonstrated. These data suggest that DA has an inhibitory effect, whereas NE has an enhancing effect on the control of LHRH secretion. In humans, these mechanisms are much more difficult to examine. Most enzyme inhibitors of catecholamine metabolism are toxic and cannot be used. DA infusions (4 µg/kg/min) have been used because of DA receptors on pituitary cells, the extra meningeal location of the gland (Leblanc et al., 1976; Lachelin et al., 1977; Judd et al., 1978) and because they significantly lower PRL and LH levels. PRL variations appear to be dependent on patient category (male, female, hyperprolactinemic), and on the day of menstrual cycle (Leblanc et al., 1976; Judd et al., 1978). LH variation is dependent on the cycle day and consequently on estrogen (Leblanc et al., 1976; Judd et al., 1978); however, FSH concentrations are less sensitive to this hormonal influence (Leblanc et al., 1976; Judd et al., 1978). Although these data demonstrate pituitary sensitivity to DA, it is difficult to demonstrate the inhibitory role of DA on gonadotropins or LH secretion. Other clinical data do not allow simple and precise conclusions. Bromocriptine, a potent DA agonist, induces a very sharp decline in PRL concentration, but does not inhibit LH release in hyperprolactinemic women (Evans et al., 1980), and has been successfully used in prolactinemic patients for treatment of anovulation and luteal insufficiency (Peillon et al., 1979). In patients who recently reached menopause, we performed a pituitary stimulation test (simultaneous 250 µg thyroid-releasing hormone and 200 µg LHRH bolus) after administration of bromocriptine or haloperidol (a DA antagonist). No variation in LH was osbserved, although PRL was inhibited by bromocriptine and stimulated by haloperidol (unpublished data). These contradictory results support the hypothesis that DA and NE modulate rather than directly influence LH and PRL levels, at least in humans. More precise pharmacologic investigations are necessary.

Present knowledge concerning other neurotransmitters and pharmacologic agents is not clear. Gamma-aminobutyric acid (GABA) and its metabolite gamma-hydroxybutyric acid (GHB) may affect gonadotropin, growth hormone and PRL secretion (Ondo, 1974; Takahara et al., 1977). Serotonin is probably involved in stimulation of PRL secretion (Boyd and Reichlin, 1978; Nathan et al., 1980), and some other pituitary hormones (Modlinger et al., 1980). The role of endogenous opiates studied both in vivo and in vitro by physiological and pharmacological methods (Bruni et al., 1977; Shaar et al., 1977; Morley et al., 1980; Quigley and Yen, 1980; Van Loon et al., 1980) indicates that they are probably modulators of these pituitary hormone secretions. However, inhibition or stimulation of these substances may be more widespread than simply affecting a group of specific neurons.

## OVARIAN LEVEL

Different physiological aspects of ovarian activity are still puzzling. Three of these, follicle development, ovarian regulation of the reproductive process, and corpus luteum evolution and lifespan, will be discussed.

### Follicular Growth and Development

Because of investigations on the control of follicular growth and development, the general process of follicular maturation is generally known. Briefly, LH and FSH stimulate follicle growth, estrogen secretion by the theca, and granulosa cell growth. In the beginning, granulosa cells divide and acquire FSH receptors, and then FSH stimulates the appearance of LH receptors. By the time of the preovulatory LH surge, the granulosa cells have enhanced ability to luteinize if removed from the follicle and cultured (Channing et al., 1978; Bjersing, 1979). Nevertheless, why one follicle grows, becomes dominant, and ovulates during each menstrual cycle remains essentially unknown. In primates and humans, only one follicle matures and ovulates; most undergo atresia, even though all follicles are exposed to the same blood level of LH and FSH. Whether the control mechanism of follicular evolution resides within the ovary itself or is dependent on gonadotropin secretion is unknown.

Several investigations in monkeys have examined the influence of gonadotropin on follicular regulation, since the hormonal processes are similar in monkeys and humans. Human menopausal gonadotropin (hMG), administered during the early or midfollicular phase, increases the number of follicles stimulated. Later in the follicular phase after a dominant follicle has developed, there is no further supplementary follicle development, and after destruction of the dominant follicle, the other follicles are temporarily

less responsive to hMG (di Zerega and Hodgen, 1980a). Under experimental conditions, selection of a dominant follicle is not altered by low FSH levels, although an increase in FSH is observed in normal cycles at the end of corpus luteum activity (di Zerega et al., 1980).

In women, the number of atretic follicles increases during the luteal phase and is considered progesterone dependent, due to quantitative and/or qualitative changes in gonadotropin secretion, or to a modified ovarian responsiveness. However, this apparent ovarian refractoriness to gonadotropin can be easily overcome (di Zerega and Hodgen, 1980b), at least in monkeys. Investigations suggest that intraovarian control of follicular function is probably important. Intraovarian sex steroids produced by the follicle itself, have been shown to play a role in this regulation in rodents, i.e. exogenous estrogen stimulates growth and prevents follicle atresia, whereas androgen inhibits these effects and promotes atresia (Louvet et al., 1975). The high levels of aromatase activity in granulosa cells and estradiol concentration in preovulatory follicles contrast with their low levels in immature and/or atretic follicles. Aromatase activity is FSH dependent, and *in vitro* is inhibited by naturally occurring androgen metabolites that have been identified in the human ovary (5-alpha-androstane-3, 17-dione; Batta et al., 1980; Hillier et al., 1980). The role of the aromatase enzyme system is supported by these investigations and participation of 5-alpha-reductase enzyme activity is suspected.

A few nonsteroidal, polypeptide, intraovarian messengers have been detected, although their role and importance have still not been determined. An oocyte maturation inhibitor able to inhibit the spontaneous resumption of meiosis, and a luteinization inhibitor have been extracted from porcine follicles (Channing, 1979). Cow and pig follicular fluids have a potent FSH inhibitory action, and castration of rats is immediately followed by a rise in FSH that cannot be suppressed by estrogen. This potent anti-FSH substance, which is also detectable in *rete testis* fluid, is called inhibin. Its polypeptide structure is not yet clearly defined.

Follicle growth regulation requires both pituitary and intraovarian messengers. Plasma levels of pituitary hormones are well known, and insufficient FSH secretion has been demonstrated in menstrual cycle disorders, especially luteal insufficiency. The role and mechanism of intraovarian factors are not sufficiently known to be used in clinical practice, although they could become contraceptive agents.

## Corpus Luteum: Luteinization and Luteolysis

Immediately after ovulation, luteinization breaks down the corpus luteum. Its constitutive process, lifespan and progressive loss of activity are still incompletely understood. Luteinization involves two different aspects of granulosa cell activity; one is biochemical (high progesterone secretion) the other is morphological (transformation) (Westwerdt et al., 1979). Many recent investigations have demonstrated that granulosa cell multiplication and evolution begin early during follicular maturation (Dimino et al., 1979) and are inhibited by follicular fluid. These cells then burst immediately after ovulation. Such a correlation in time indicates that the corpus luteum quality and lifespan are dependent on follicular growth (Vande Wiele and Turksoy, 1965). It is presently thought that corpus luteum activity is dependent on luteotropic factors (Niswender et al., 1972; Ross and Hillier, 1978). Among these, the role of PRL is controversial (McNatty 1979a,b), but that of LH is essential. From the time of LH peak, progesterone is preferentially secreted compared with 17-OH-pregnenolone, multiplication of granulosa cells stops and their transformation into luteinized cells is enhanced (Thibault and Levasseur, 1979). Accessory luteotropic factors include estradiol (at least in rats) and prostaglandins of the E type (Thibault and Levasseur, 1979).

The corpus luteum lifespan is 14 $\pm$ 2 days in women. Its regression begins a few days earlier and is marked by a progressive or precipitous decline in progesterone secretion. "Regression of the corpus luteum is pivotal in regulating the estrous and menstrual cycle since it permits follicular development and the ovulatory surge of pituitary gonadotropins in the subsequent cycle." (Behrman et al., 1979).

The first demonstration of luteolysis was the influence of hysterectomy and endometrium-secreted prostaglandin $F_{2\alpha}$ in the rat, sheep, and horse. After hysterectomy, corpus luteum activity is maintained; endometrial ablation has the same effect due to the anatomical position (ipsilateral) of the uterine vein and the ovarian artery (Thibault and Levasseur, 1979). The influence of endometrium-secreted prostaglandin is demonstrated by its high concentration in the uterine vein and the opposite effect of indomethacin upon injection into the uterine horn (Thibault and Levasseur, 1979). Recently, different cellular aspects of this luteolytic mechanism have been set forth: prostaglandin $F_{2\alpha}$ impedes gonadotropin uptake *in vivo* and *in vitro*, the adenylate complex is no longer observed and LH binding is reduced (Behrman et al., 1979).

In primates, the cellular mechanism is probably similar, since prostaglandin receptors have been demonstrated (Powell et al., 1974); however, the physiological mechanism is different, as endo-

metrial prostaglandins (Singh et al., 1975) cannot reach the ovary directly, and it is estradiol dependent (Auletta et al., 1978). In cattle and probably primates, progesterone, estradiol and prostaglandin are produced by the same cell (Shemesh and Hansel, 1975). Nevertheless, in primates prostaglandin $F_{2\alpha}$ and indomethacin produce no physiological or clinical effect.

Another cellular mechanism that contributes to luteolysis regulation is cell desensitization or down-regulation, which is concerned with regulation of peptide hormone receptors and target cell responses due to increased concentrations of homologous hormone (Catt et al., 1979). This process assists in the regulation of receptor sites in target cells by polypeptide hormones and is particularly marked in the testis and ovary after exposure to elevated gonadotropin levels. In the rat ovary, it follows several successive phases (Catt et al., 1979). The early phase of receptor site occupation is characterized by acute biological stimulatory responses (1 min to 3 hr ), activation of adenylate cyclase, generation of cyclic AMP, and production of progesterone. During the late phase of site occupation, the primary refractory state begins (6 hr ), the number of free sites, adenylate cyclase responsiveness, cyclic AMP response, and progesterone production decrease. The secondary refractory state (1 to 4 days) is characterized by the loss of LH receptors, loss of adenylate cyclase stimulation, and loss of cyclic AMP response and progesterone secretion. A recovery period follows this refractory state and lasts 3 to 10 days (Catt et al., 1979). LH receptors are probably effective only once, and then are degraded by intracell resorption and "internalization" (Catt et al., 1979; Lindner, 1979).

In summary, continued exposure of ovarian cells to gonadotropins or prostaglandin results in a characteristic sequence of events: (1) increased cyclic AMP formation; (2) progressive desensitization of the adenylate cyclase system, attended or followed by down-regulation of receptor density on the cell surface; and (3) gradual recovery of responsiveness upon removal of the hormone (Lindner, 1979).

This membrane regulatory mechanism appears to be of great importance in luteolysis and could also participate in corpus luteum maintenance. Pulsatile LH secretion would be significant as each LH pulse would determine the occupation of a few binding sites, their clustering, and their degradation by "internalization", and the loss of a few receptor sites. The disappearance of successive sites would stimulate continuous receptor synthesis. If this hypothesis is correct, repeated tiny desensitizations would have great importance in corpus luteum activity (Lindner, 1979).

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