Progress in GYNECOLOGY

Volume VII

Taymor and Nelson
Editors

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GRUNE & STRATTON
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York London Paris
San Diego San Francisco São Paulo
Sydney Tokyo Toronto

Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Distributed in the United Kingdom by
Grune & Stratton, Inc. (London) Ltd.
24/28 Oval Road, London NW1

Library of Congress Catalog Number MED47-743
International Standard Book Number 0-8089-1587-8
Printed in the United States of America

Preface

The years that have passed since publication of the last edition of *Progress In Gynecology* have been a time of consolidation of the advances of the past and exciting exploration along new frontiers. The separation of obstetrics and gynecology into the three subdivisions of oncology, reproductive endocrinology, and perinatology, despite the drawbacks that super-specialization imposes, has created a breed of clinical scientists who have the focus, the background, and the backing to push onward.

In the field of reproductive endocrinology, a veritable microscope is being held up to the details of the union between the sperm and egg and to the mechanisms that control this phenomenon in the brain, the pituitary, and the ovaries. As a result, our knowledge of normal and abnormal menstrual physiology has been greatly enhanced, and our ability to treat abnormal physiology, that is, anovulation, polycystic ovaries, galactorrhea, has been rendered more effective. The culmination of this advancing knowledge has brought us close to the time when in vitro fertilization and embryo transfer may well be a routine approach to the treatment of many of the aspects of infertility. The microscope, in a more literal sense, has been brought to bear upon surgical technique. Fine "microscopic" technique, if not the microscope itself, has been shown to be of enormous importance in not only tubal reconstructive surgery but also in surgery involving all patients in the reproductive years. In the area of oncology and gynecologic surgery, a close look has been taken at standard forms of therapy, and significant advances have been made: the laser for treating benign cervical lesions, prophylactic antibiotics, and integrated treatment for endometrial carcinoma and for urinary stress incontinence.

As a result of the above, we can feel that the effort to bring these advances to a single volume is well justified. We are grateful to our many colleagues, outstanding in their diverse contributions to our specialty, who have given of their time and wisdom to make this volume possible. We remain ever grateful to our two teachers, Joe Vincent Meigs and Somers H. Sturgis, whose original idea continues to bear such important fruit. Once again, we acknowledge the contributions of Jan Wohlberg, who had the task of collecting, collating, and monitoring the manuscripts from authors to editors to publisher, a difficult enterprise that she handled with good humor, energy, and efficiency.

Contents

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PART I

Growth and Physiology

Judith L. Vaitukaitis

1

Neuroendocrine Control of Gonadotropin Secretion in Women

The normal menstrual cycle reflects the integrated physiologic effects of several hormones, neurotransmitters, and releasing and inhibiting factors secreted by the hypothalamus, the pituitary, and the ovaries. Probably the most important modulators of gonadotropin secretion are sex steroids secreted by the ovaries and gonadotropin-releasing hormone (GnRH), a decapeptide that is synthesized and secreted by hypothalamic peptidergic neurons. Over the past 15 years not only have sensitive radioimmunoassays been developed to measure physiologic levels of circulating hormones, but also purification techniques have been devised to ascertain the specific amino acid sequences of gonadotropins as well as peptides isolated from hypothalamic nuclei. Additionally, a variety of new pharmacologic agents have been identified that affect gonadotropin secretion by interacting with hypothalamic sites or with the pituitary. These agents provide probes with which investigators can gain insight into the hypothalamic-pituitary control of gonadotropin secretion.

Hormones undergo pulsatile secretion. This results in changing concentrations of the circulating hormones, which is termed "circhoral" variation. The term "circhoral" was coined to describe the approximately hourly variations in the levels of circulating gonadotropins. The higher the blood gonadotropin levels, the greater the amplitude of the hourly change in circulating gonadotropin concentration.

Supported in part by General Clinical Research Center Grant RR-533. Division of Research Resources, National Institutes of Health

Although considerably more data exist on the neuroendocrine control of gonadotropin secretion in subprimates, the present discussion will focus almost exclusively on observations in women and in subhuman primates. The menstrual cycle of subhuman primates closely approximates that of normal women. Moreover, evidence suggests that the neuroregulatory control of gonadotropin secretion of subprimates differs significantly from that of primates.

GONADOTROPINS

The human pituitary gonadotropins—luteinizing hormone (LH) and follicle stimulating hormone (FSH)—are glycoproteins that share a common quaternary structure in which there are two different noncovalently linked subunits, designated alpha and beta.[18] Another anterior pituitary hormone, thyrotropin, and the placental hormone, chorionic gonadotropin (hCg), are also glycoproteins composed of alpha and beta subunits. The alpha subunits of these hormones have essentially identical amino acid sequences but the amino acid sequences among the beta subunits differ considerably and confer both immunologic and biologic specificity to the hormones. Both LH and hCG share indistinguishable biologic activities, reflecting the extensive structural homology between their beta subunits. The plasma half-lives of the pituitary gonadotropins are relatively short and average 30–40 minutes, but the plasma half-life of hCG is of the order of 24–36 hours. The plasma half-lives of the free subunits of pituitary gonadotropins are short, less than 15 minutes. When circulating levels of the gonadotropins are high, small but significant concentrations of free alpha subunits are readily measurable. Free alpha and beta subunits are devoid of significant intrinsic biologic activity. Extracts of normal pituitary and placenta contain significant concentrations of free alpha subunits. The physiologic significance of the free alpha subunit is unknown.

Immunocytochemical studies suggest that fetal pituitary synthesis of the alpha subunit begins before that of the entire glycoprotein hormones.[6] Immunoreactive alpha subunit is detectable within the fetal pituitary as early as 2 months after conception, and shortly thereafter, immunoreactive FSH and LH appear within pituitary cells or gonadotropes. Some studies suggest that both LH and FSH are synthesized in the same pituitary cell, while other studies suggest that LH and FSH are synthesized in separate cells. Extracts of female fetal pituitaries contain markedly increased concentrations of immunoreactive FSH between the 20th and 34th weeks of gestation; this is accompanied by a significant but less striking increase in pituitary LH concentrations. Interestingly, peak circulating female fetal serum FSH levels are observed at midgestation at levels comparable to those of menopausal women. After that point in the course of gestation, serum FSH levels decrease and that decrease coincides with onset of fetal ovarian follicular development.[11] These observations support the establish-

ment of negative feedback between the hypothalamic-pituitary-ovarian axis by midgestation in the female fetus. That feedback mechanism between the hypothalamic-pituitary-ovarian axis remains operative for the remainder of an individual's lifespan but with changing sensitivities.

At term, fetal serum LH and FSH levels are very low or undetectable. Shortly thereafter, serum FSH and LH levels increase moderately, and that increase is accompanied by a moderate increase in circulating estradiol levels because of gonadal stimulation by endogenous gonadotropins[20]. That increase in circulating gonadotropins and estradiol persists for the first 2 to 4 years of postnatal development. The mechanisms responsible for the increased circulating levels of gonadotropins are unknown. After these first few years, circulating levels of gonadotropins and estradiol decrease and remain at low levels until puberty approaches.[20]

PUBERTY

With the onset of puberty, sleep-induced release of gonadotropin is observed and is correlated with sleep stage.[10] Figure 1 depicts the circulating gonadotropin levels along with stages of sleep. The precise mechanism governing the sleep-induced release of gonadotropins in humans is unknown, and the release is no longer observed after the completion of puberty, which takes 3 to 5 years. An inhibitory effect of sleep on LH secretion has been observed in normal women studied during the early follicular phase. Sleep reversal studies have confirmed that the change in LH secretion is sleep-related. Moreover, the sleep-induced suppressive effects on LH secretion are more marked among women with hypothalamic amenorrhea.

When prepubertal female monkeys are subjected to intermittent pulsatile infusions of exogenous GnRH, ovulatory menstrual cycles may be induced. These observations suggest that puberty may be accompanied by the onset of endogenous pulsatile release of GnRH, which in turn stimulates increased pituitary gonadotropin synthesis and secretion and subsequent ovarian follicular development with a consequent increase in the synthesis and secretion of gonadal sex steroids. The mechanism responsible for initiation of the putative pulsatile GnRH secretion with puberty is unknown.

Since GnRH secretion is needed for both pituitary synthesis and secretion of gonadotropins before puberty, the frequency and amplitude of GnRH secretion must be modified during puberty to account for increased circulating levels of gonadotropins. Other hypothalamic centers modulated by monaminergic neurons connected to higher neural centers probably affect the sleep-induced increase in GnRH secretion. These pathways, however, have not yet been identified.

As puberty approaches, there is a small but significant progressive increase in circulating FSH levels initially, followed by a small but significant rise in the level of LH. Before the completion of puberty, estrogens exert only a negative

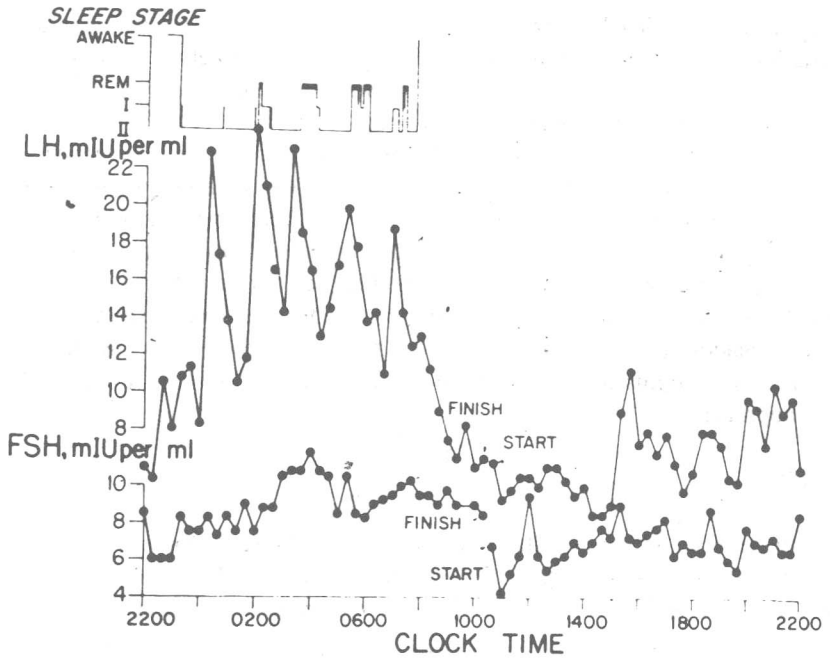

Fig. 1. Serum LH and FSH concentrations of a girl undergoing spontaneous puberty during nocturnal sleep and during the day. Sleep stage is indicated at the top of the figure. [Reprinted from Boyar RM, Finkelstein JW, David R, Roffwarg H, Kapen S, Weitzman ED, Hellman Z,Twenty-four hour patterns of plasma luteinizing hormone and follicle stimulating hormone in sexual precocity. By permission of the New England Journal of Medicine 289:282–286 1973.]

feedback effect on gonadotropin secretion. With pubertal progression, however, estrogens exert both a negative and positive feedback effect on gonadotropin secretion. The anatomic sites responsible for the differential estrogen effects are unknown.

Progressively increasing levels of sex steroids induce development of secondary sexual characteristics, e.g., breast development, growth of pubic and axillary hair, change in body fat distribution, that are normally associated with pubertal development. Menarche, or the onset of spontaneous menses, is but one phase of pubertal development. The onset of menarche appears to be correlated with body fat composition. However, how body composition directly or indirectly affects neuroendocrine control of gonadotropin secretion is undefined. Moreover, the estrogen-induced positive or negative feedback effects on gonadotropin secretion vary depending upon the circulating level of estrogen as well as the duration of exposure.

MENSTRUAL CYCLE

In women during their reproductive years, the median intermenstrual interval is approximately 28 days.[17] However, marked variation in that interval is observed for the first few years after spontaneous menarche and for several years before the cessation of menses and the completion of menopause. Both extremes of the reproductive life cycle are accompanied by a high frequency of anovulatory cycles. As women approach their late 20s and early 30s, the intermenstrual interval decreases by a few days[17]. The normal menstrual cycle is divided into two parts, the follicular and luteal phases. The luteal phase is the most fixed part of the menstrual cycle and normally averages 12 to 14 days. The follicular phase, on the other hand, is the more variable part of the menstrual cycle. Figure 2 depicts the mean circulating levels of gonadotropins and sex steroids during normal presumptively ovulatory menstrual cycles. During the follicular phase there is a small but progressive rise in circulating LH levels. In contrast, circulating FSH levels increase during the first half of the follicular phase, usually signaling the midcycle or preovulatory surge of gonadotropins. The follicle destined to become the graafian follicle is selected during the mid follicular phase and that follicle becomes the major source of estradiol during the late follicular phase. Within 12 to 36 hours of the surge of gonadotropins, ovulation occurs. The preovulatory surge of gonadotropins signals the onset of the second half of the menstrual cycle or the luteal phase. During the luteal phase, circulating levels of both LH and FSH decrease and their mean levels are usually lower than the gonadotropin levels during the first half of the menstrual cycle. If conception does not occur within a cycle, the circulating levels of FSH increase for the last few days of the luteal phase and that increase is carried over to the first half of the following follicular phase. Sex steroids and probably several hypothalamic peptides and neurotransmitters modulate the cyclic release of gonadotropins of normally cycling women.

During the first several days of the follicular phase, estradiol exerts a negative feedback effect on both LH and FSH secretion. After that time, estradiol exerts a positive feedback effect on LH release during the follicular phase but continues to exert a negative feedback effect on FSH secretion for most of the remaining follicular phase. Estradiol levels increase significantly in the late follicular phase.

A critical concentration and duration of exposure of estradiol contribute to triggering the midcyle or preovulatory surge of gonadotropins. Using a subhuman primate model, Knobil's[12] laboratory reported that the midcycle or preovulatory surge of gonadotropins may be induced with a critical concentration and duration of exposure of estradiol in rhesus monkeys having a surgically interrupted neural connection between the medial basal hypothalamus and the remainder of the central nervous system. The mechanism by which estradiol contributes to the midcycle or preovulatory surge of gonadotropins in women is poorly understood at this time but may reflect interaction both directly with the pituitary itself as

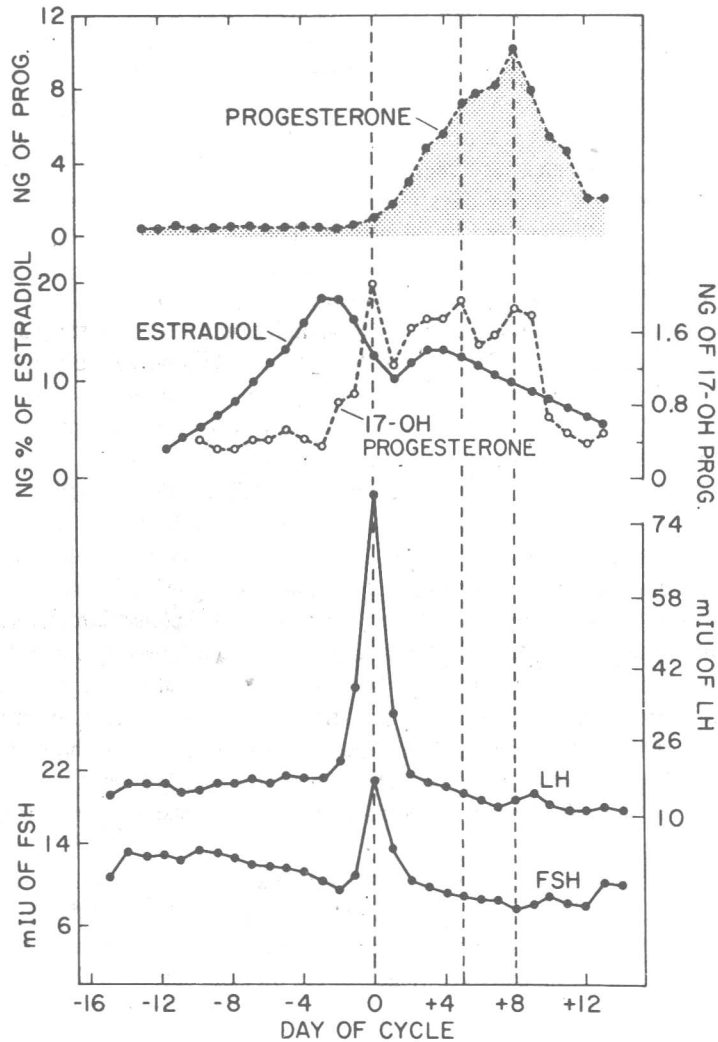

Fig. 2. Circulating levels of LH, FSH, and 17-hydroxyprogresterone per milliliter of serum and estradiol in nanograms per 100 ml of serum in normally cycling young women. Concentrations are synchronized with the midcycle LH surge. [Reprinted from Vaitukaitis JL, Ross GT Clinical Studies gonadotropin in the female: Pharmacol Ther [C] 1:317–329, 1976. With permission.]

well as with hypothalamic sites where estradiol may interact with GnRH and other neurons.[4,12]

The granulosa cells of the developing graafian follicle secrete not only estradiol but also 17-hydroxyprogesterone in the late follicular phase. Peak levels of circulating 17-hydroxyprogesterone are observed just before or simultaneously with the midcycle surge of gonadotropins and are observed 24 to 48 hours later than peak levels of circulating estradiol in the later follicular phase.

After ovulation, the remainder of the graafian follicle is luteinized by LH and transformed into a corpus luteum, which secretes progesterone, estradiol, and 17-hydroxyprogesterone in women. As progesterone levels rise, an increase in basal body temperature is observed and reflects the interaction of progesterone with hypothalamic sites, which in turn results in an increased core body temperature. As progesterone and estradiol levels increase during the luteal phase, circulating levels of LH and FSH decrease significantly. Circulating levels of gonadotropins during the luteal phase are characterized by low frequency high-amplitude spikes in contrast to the high frequency low-amplitude spikes of gonadotropins during the follicular phase.

During the normal menstrual cycle, increased concentrations of circulating 17-hydroxyprogesterone and estradiol are observed in the late follicular and midluteal phases. The first peak reflects granulosa cell secretion whereas the second, lower peak reflects secretion by the corpus luteum.

GONADOTROPIN-RELEASING HORMONE SECRETION

Gonadotropin-releasing hormone is a decapeptide initially isolated from ovine and porcine hypothalami. Gonadotropin-releasing hormone stimulates pituitary cells to synthesize and secrete LH and FSH. Studies in rhesus monkeys provide strong evidence for the pulsatile release of GnRH into portal blood. The highest hypothalamic GnRH concentrations are probably present in the arcuate nucleus. The LH response induced is usually greater than the FSH response induced by GnRH in normally cycling women studied during any phase of the menstrual cycle. The GnRH binds to specific plasma membrane receptors of its pituitary target cells with subsequent activation of adenylate cyclase. There appear to be two pools of gonadotropins within the pituitary, a readily releasable pool observed within the first hour of GnRH infusion and a second pool that probably reflects stored and newly synthesized gonadotropins. Figure 3 depicts circulating gonadotropin levels during a continuous infusion of synthetic GnRH (generously provided by Parke-Davis) among normally cycling women studied during the early follicular phase. Interestingly, in spite of the continued infusion of GnRH, circulating levels of LH and FSH decrease over the last several hours of the infusion, probably reflecting desensitization of gonadotropes to the effects of GnRH. The integrated GnRH-induced LH response is significantly greater than that for FSH among normally cycling women. However, among prepubertal

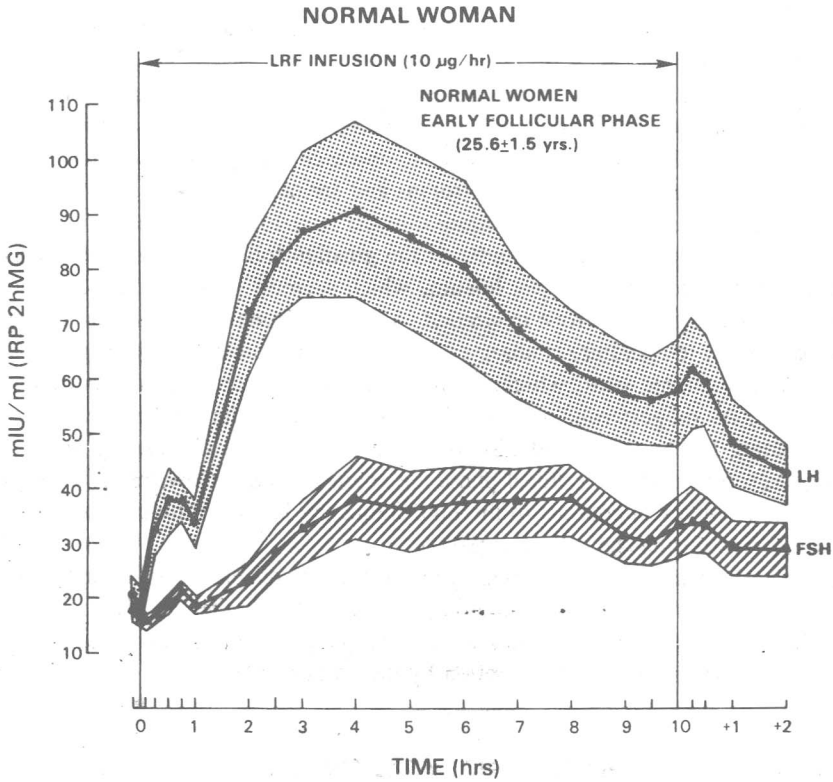

Fig. 3. Circulating levels of LH and FSH before during and after a continuous infusion of synthetic GnRH. Hormone concentrations were determined by specific radioimmunoassay with IRP2LMG serving as the reference preparation. Shaded areas encompass the mean ± 1 SEM. [Reprinted from Griffing G, Redline R, Jaffee W, Longcope C, Vaitukaitis J: Effect of peripheral sex steroid metabolism on pituitary gonadotropin reserve of women with hypothalamic amenorrhea. Fertil Steril 36:578, 1981. With permission of the publisher, The American Fertility Society.]

girls, castrated women, and women with hypothalamic amenorrhea with low estradiol levels, the GnRH-induced FSH response may exceed that for LH.[8] Those settings reflect decreased estradiol secretion, which may differentially affect pituitary LH and FSH synthesis. When pituitary cells are maintained in culture in the absence of estradiol and GnRH, FSH may be synthesized and secreted autonomously but LH synthesis and secretion usually decreases. However, if estrogen is added to the culture medium, FSH synthesis decreases. These observations suggest that FSH, unlike LH, may be secreted autonomously by pituitary cells removed from the control of the hypothalamus and sex steroids.

When normally cycling rhesus monkeys are subjected to selective destruc-

tion of the arcuate nucleus and subsequently stimulated with synthetic GnRH through an intermittent infusion of 1 μg/min for 6 minutes every hour and maintained for several weeks, cyclic release of gonadotropins and sex steroids indistinguishable from that observed during the spontaneous menstrual cycles of intact monkeys, is observed.[12] Moreover, when the GnRH infusion is discontinued, both gonadotropin and sex steroid levels decrease precipitously and the positive feedback effect of estradiol on gonadotropin secretion is abolished. Women with hypothalamic amenorrhea respond similarly to low dose pulsatile GnRH stimulation with onset of cyclic gonadotropin and sex steroid secretion.[5] Paradoxically, when GnRH is infused tonically, the pituitary becomes resistant to the decapeptide. In addition, GnRH exerts a direct inhibitory effect on gonadal steroidogenesis, although the arcuate nucleus probably does not secrete sufficient concentrations of GnRH into peripheral blood to affect the gonads directly. However, several GnRH analogue are currently undergoing investigation as potential contraceptive agents.

The area of the arcuate and median eminence of the hypothalamus is enriched with GnRH, dopamine, and β-endorphin neurons. Gonadotropin-releasing hormone is secreted directly into portal capillaries and delivered by the portal circulation to the gonadotropes. Just as gonadotropins are released in pulsatile fashion into the peripheral circulation, GnRH is probably delivered in pulses to pituitary cells through the portal circulation in humans; such a system has been noted in monkeys. The modulation of GnRH secretion by hypothalamic peptidergic neurons is poorly understood. Several lines of evidence, however, suggest modulation of GnRH secretion by a variety of neurotransmitters and polypeptides. In rhesus monkeys, phentolamine, an alpha-adrenergic blocking agent, inhibits GnRH release. Whether alpha-adrenergic control modulates gonadotropin secretion among normally cycling women or among women with altered hypothalamic-pituitary function is undefined.

Experimental evidence in rhesus monkeys suggests that estradiol exerts its negative feedback effect on gonadotropin secretion by directly interacting with pituitary gonadotropes; this effect is independent of its interaction with GnRH neurons.[4,12] Moreover, studies in normally cycling women strongly suggest that estradiol modulates the sensitivity of pituitary gonadotropes to exogenous GnRH. When the same dose of synthetic GnRH is administered in a bolus to normally cycling women in th early and late follicular phase, a greater GnRH-induced gonadotropin response is observed in the late follicular phase when circulating estradiol levels are highest. Administration of estrogens to normally cycling women for several days in the early follicular phase enhances their GnRH-induced gonadotropin response, similar to the responses observed in the late follicular phase. Figure 4 depicts GnRH-induced responses among normally cycling women studied in the early follicular phase with and without estrogen pretreatment. Interestingly, in rhesus monkeys that have undergone ablation of the arcuate nucleus and are consequently free of endogenous GnRH stimulation, the estro-