Hormonal Levels During the Early Follicular Phase of the Menstrual Cycle

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Hormones from the pituitary and ovaries are largely responsible for follicular growth and development. An understanding of the cyclic changes in these hormones throughout the normal menstrual cycle may be of use in monitoring hormone levels in women undergoing assisted reproduction.

A normal menstrual cycle lasts about 28 days. It consists of two phases: the follicular phase (also called the proliferative phase or estrogenic phase), and the luteal phase. The first day of menstruation is considered to be day 1 of both the menstrual cycle and the follicular phase. Menstruation marks the luteal-follicular transition and continues throughout the first few days of the follicular phase. The ovulatory period, sometimes called the midcycle phase, marks the follicular-luteal transition. This period normally occurs about 14 days after the onset of menstruation.

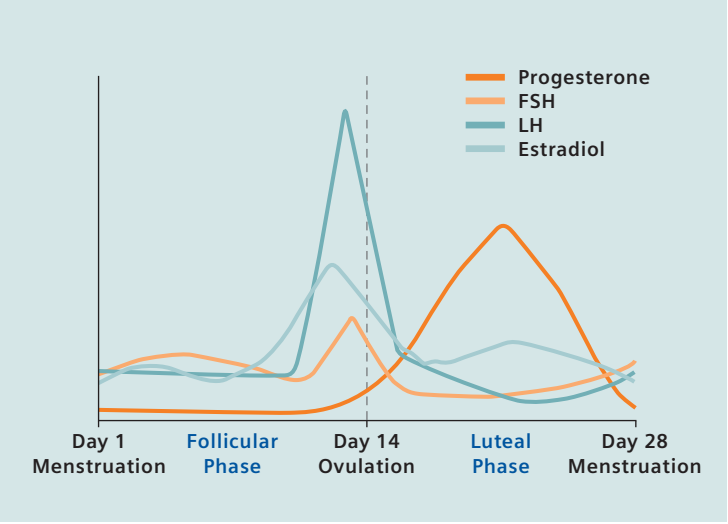
The fetal ovary contains about 6 million oocytes surrounded by a single layer of cuboidal cells, called primordial follicles.[1] This number is important because no additional oocytes are produced after the fetal period. During each menstrual cycle, some of these primordial follicles are selected to develop into primary follicles. Throughout the reproductive years, a number of these follicles grow and mature up to ovulation during the follicular phase of each reproductive cycle. From the initial ovarian reserve, only about 400 follicles are selected to develop through ovulation. This selection process is not yet understood and seems to be independent of gonadotropins. Follicle-stimulating hormone (FSH) is considered to be the dominant stimulating factor for follicular growth and development. Follicles that do not develop become atretic.

Follicular Development and the Follicular Phase

The different stages of follicle growth are classified into the primordial, primary, preantral, antral, preovulatory and mature stages. It is estimated that it takes a primordial follicle 85 days to reach the preovulatory stage. Follicles are developed during the follicular phases of subsequent menstrual cycles. During this first stage of follicular growth and development, the oocyte is surrounded by a poorly defined layer of granulosa cells and a small number of theca cells. Preantral follicles are oocytes surrounded by two to eight layers of granulosa cells. As follicular maturation progresses, the proportion of theca cells increases in the follicle until a fully developed layer is formed. At the antral stage, fluid- containing follicles are approximately 3 mm in diameter. The penultimate stage in follicular development is the preovulatory follicle, which is similar to the antral follicle, but with rapidly expanding dimensions (days 13 to 15 of a normal cycle). At this stage, an oocyte is moved to one side in the follicle. It is surrounded by many layers of granulosa cells, which are called the cumulus cells after ovulation.

Each follicle is developed individually rather than in groups. The follicle that is selected to mature fully up to ovulation is slightly more advanced and slightly larger than the nearby follicles that are not selected to mature. The follicle that proceeds through ovulation is thought to contain a larger number of granulosa cells.

Figure 1. Hormonal Profiles Throughout the Menstrual Cycle



The monthly menstrual cycle prepares an egg for maturation, ovulation and fertilization. The human menstrual cycle comprises three phases:

Follicular Phase – initiates the growth and maturation of an ovarian follicle, which actually begins during the last few days of the previous Luteal Phase.

Ovulatory Phase – the interval in which the LH surge induces ovulation.

Luteal Phase – the last portion of the cycle that prepares the endometrium for implantation of a fertilized ovum.

Follicular development is regulated by pituitary gonadotropins, ovarian steroids, and peptide hormones that are produced in granulosa and/or theca cells. These hormones may be involved in selection and maintenance of a dominant follicle through autocrine, paracrine, or endocrine effects, including effects on other endocrine glands. Inhibin, activin, follistatin, and insulin-like factors are peptides responsible for regulating follicular growth. Granulosa cells are the first to respond to rising follicle-stimulating hormone (FSH) levels during the first days of the follicular phase. Follicles secrete androstenedione, which is aromatized into estradiol. Enhanced estradiol production stimulates granulosa cell development through inhibin, which results in a drop of the FSH production, preventing the additional development of follicles. Although inhibin is a marker used to evaluate follicular reserve, FSH is responsible for inducing granulosa cells to develop and increase production of estradiol.

Ovulation and the Luteal Phase

At ovulation, a mature follicle (approximately 18 mm in diameter) ruptures in response to a surge of LH, releasing a mature oocyte (ovum). The luteal phase, also called the secretory phase or progestational phase, starts just after ovulation. During this phase, the granulosa cells constitute the corpus luteum. They secrete progesterone and E2 in conjuction with theca cells. The corpus luteum remains for about 14 days if no pregnancy occurs.

Hormone Levels During the Luteal-Follicular Transition

If pregnancy does not occur, an increase in FSH is observed 3 to 4 days before the luteal-follicular transition. It is concomitant with lysis of the corpus luteum and with an associated decrease in progesterone and estradiol levels. Hormonal fluctuations of FSH, estradiol, and progesterone during the last days of the luteal phase and the first days of the follicular phase are shown in Figure 1. During this time, the levels

of FSH are generally lowest near the end of the luteal phase, and generally highest during the early follicular phase. In a study of reproductive hormone levels in 54 normally cycling volunteers, daily serum samples were collected throughout the menstrual cycle. Table 1 shows day 2 and day 3 levels of FSH, estradiol, and progesterone. During the early follicular phase, FSH is responsible for follicular development as described above. During the mid-follicular phase, increased estradiol levels and decreased FSH levels correspond to the selection of a dominant follicle.

Early Follicular Phase Hormonal Levels in Normally Cycling Women and in Women Undergoing Assisted Reproduction

FSH and estradiol are measured from cycle day 2 through day 5 in order to evaluate the ovarian reserve and to investigate the variability between the menstrual cycles in normally cycling women. Day 2 and day 3 measurements of FSH and estradiol, combined with maternal age, are useful for predicting pregnancy outcome. These measurements are standard practice for predicting oocyte quality and the likelihood of conception in assisted reproductive technologies (ART).

Basal (cycle day 3) FSH and LH have a strong predictive value that is useful for choosing a cycle for controlled ovarian hyperstimulation.[2] If FSH levels do not exceed LH values on cycle day 3, the outcome is more likely to be successful.

In a study of patients undergoing in vitro fertilization (IVF), pregnancy rates were decreased significantly at FSH levels greater than 15 mIU/mL at cycle day 3.[4,5] In another study of 592 patients undergoing controlled ovarian hyperstimulation in which a gonadotropin releasing hormone was not used, oocyte numbers and pregnancy rates were the highest in patients with the lowest FSH and estradiol levels.[6] Pregnancy rates were lower when FSH levels were greater than 17 mIU/mL, and estradiol levels were greater than 45 pg/mL. (Such results would normally be interpreted, however, in the context of the range of the obtained FSH levels, which were not given.)

The relationship between serum estradiol levels and the outcome of ART procedures is dependent on the study. In a treatment protocol by Smotrich et al., patients were given luteal-phase gonadotropin-releasing hormone for pituitary suppression and human menopausal gonadotropin for

Table 1. Serum FSH and estradiol levels in 54 apparently normally cycling, ovulating women during the early follicular phase (ND = nondetectable).

	Day 2 and day 3 values	
	Median	Central 95%
FSH, mIU/mL	6.6	3.0 – 14.4
Estradiol, pg/mL	31	ND – 84
Estradiol, pmol/L	114	ND – 308

Results are based on a Siemens study conducted on healthy adults age 20 and over (81 females, 87 males).

Table 2. FSH levels (mean ± SEM) in 29 normally cycling women during the early follicular phase.

Cycle day	FSH (mIU/mL)
2	5.7 ± 1.9
3	5.9 ± 2.1
4	6.3 ± 2.4
5	6.3 ± 2.5

Table 3. Success rates of in vitro fertilization according to day 3, serum estradiol levels (PR = pregnancy rate).

	Estradiol< 80 pg/mL	Estradiol 80 pg/mL	P*	Estradiol> 100 pg/mL
Number of cycles	265	27	–	15
Cancellation rate per initiated cycle (%)	0.4	18.5	<0.0001	33.3
Clinical PR per initiated cycle (%)	37.0	14.8	0.02	0
Day 3 FSH (mIU/mL)†	8.1 ± 0.3	5.7 ± 0.5	0.01	6.6 ± 0.7

* Estradiol < 80 pg/mL versus 80 pg/mL.
† mean ± SEM.

Table 4. IMMULITE results for patients with estradiol levels less than 80 pg/ml (less than 294 pmol/L) at day 2 and day 3.

	Mean	Median	Central 95%
Age (years, n = 133)	35.6	36.0	23 – 46.2
FSH (mIU/mL, n = 96)	7.0	6.2	2.27 – 17.2
LH (mIU/mL, n = 124)	3.8	3.5	< 0.70 – 10.0
Progesterone (ng/mL, n = 123)	0.64	0.59	0.29 – 1.30
Progesterone (nmol/L, n = 123)	2.03	1.88	0.92 – 4.13
Estradiol (pg/mL, n = 121)	33.9	32.5	< 20 – 70.2
Estradiol (pmol/L, n = 121)	125	119	< 73.4 – 258
Prolactin (ng/mL, n = 120)	15.4	12.5	4.05 – 41.9
Prolactin (mIU/L, n = 120)	327	265	85.9 – 888

Table 5. Various parameters grouped according to serum estradiol levels on the day of oocyte donation (NS = not significant).

	Estradiol (pg/ml)					
	<100	100 - 199	200 - 299	300 - 399	400	
Cycles	26	134	115	84	106	–
Number of oocytes	7.6	6.9	8.1	8.6	8.3	NS*
Rate of fertilization (%)	74.9	69.1	66.9	68.1	68.3	NS*
Number of embryos transferred	4.4	4.1	3.9	4.0	3.9	NS*
Pregnancy to transfer ratio (%)	12.2	19.0	21.0	14.7	16.7	NS†
Total implants	12.2	19.0	21.0	14.7	16.7	NS*

* ANOVA.
† Chi-squared.

ovarian stimulation.[7] Patients with a day 3 estradiol level greater than or equal to 80 pg/mL had a higher cancellation rate and achieved a lower pregnancy rate. Pregnancy did not occur in patients with day 3 FSH levels of at least 15 mIU/mL. Day 3 estradiol levels, in addition to day 3 FSH levels, appeared to be very helpful in prospectively counseling patients regarding cancellation risks and the success of IVF embryo transfer. (See Table 3) In a study[4] by Jiménez et al., patients were given estradiol valerate before egg donation. In contrast to the results by Smotrich et al., serum estradiol levels on the day of oocyte donation were not indicative of the number of eggs harvested, rate of fertilization, number of embryos transferred, ratio of the number of pregnancies to the number of embryos transferred, or rate of implantation.[8] (See Table 5)

In a study by Diamond et al., a larger number of hormones were measured in a total of 133 patients during the early phase of the normal menstrual cycle.[9] FSH, LH, prolactin, estradiol and progesterone serum levels were measured using IMMULITE® kits at day 2 or day 3 in sera of patients scheduled to undergo ART. (See Table 4) The data from this study were similar to results for the early follicular phase of IMMULITE reference range data, which are shown in Figure 1.

Conclusions

Follicular growth and development are regulated by several hormones from the pituitary and the ovaries. An understanding of cyclic changes in reproductive hormones throughout the normal menstrual cycle may be useful for understanding the value of monitoring these hormonal levels in women who receive assisted reproduction. FSH and estradiol are common choices for monitoring during the early follicular phase of women receiving ovarian hyperstimulation and IVF. Levels of these hormones are then evaluated with respect to the achievement of pregnancy.

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