THE MENSTRUAL CYCLE

P. Mock

Infertility and Gynecologic Endocrinology Clinic

Geneva University Hospital

INTRODUCTION

In women, the fertile period starts at the menarche (first menstrual period) and ends with the menopause. This period is divided in cycles of 28 to 35 days in length separated by menstruation. It is more by convenience than by physiological truth that the cycle starts on the first day of menstruation and ends on the day preceding the next menstruation.

The cycle is divided in two periods of unequal length: the phase that precedes ovulation (or follicular rupture) is called the *follicular phase* whereas the period which follows ovulation is termed the *luteal phase*.. The length of the follicular phase depends on the velocity of growth of the ovarian follicles and is thus variable from one woman to another. In contrast, the length of the luteal phase depends on the life span of the corpus luteum, it is thus less variable. In the 20 women whose hormonal results are presented below, the mean duration ($\pm$ SD) of the follicular phase was 15.4 $\pm$ 2.5 days and the mean duration of the luteal phase was 13.6 $\pm$ 1.2 days).

THE HORMONES OF THE MENSTRUAL CYCLE

The ovarian cycle is part of an integrated system which includes the hypothalamus, the pituitary, the ovary and the uterus (Fig. 1). The biological clock which is responsible for the rhythmicity of the cycles consists in the pulsatile release of an hypothalamic decapeptide: the Gonadotropin Releasing Hormone (GnRH). The pulsatile secretion of GnRH depends not only on external events (psychological factors or the nyctaehemeral rhythm) which reach the hypothalamus from the cortex through the limbic system but depends also on the ovarian events through the feed-back effect that the sexual steroids exert on the hypothalamus and the pituitary. This modulated secretion of GnRH controls the release and synthesis of the polypeptidic pituitary gonadotropins: *Follicle Stimulating Hormone* (FSH) and *Luteinising Hormone* (LH).

FSH allows recruitment and growth of the ovarian follicles as well as the selection of the dominant follicle whereas LH induces follicular rupture and sustains the corpus luteum. *Oestradiol* and *Progesterone* are produced respectively by the follicles and the corpus luteum where their secretion is gonadotropin-dependent. Bound to transport proteins, these steroids are carried in the blood stream and regulate the secretion of GnRH, FSH and LH and induce proliferation and differentiation of the uterine endometrium in order to guarantee implantation of the embryo if fertilisation has taken place.

THE REGULATION OF THE MENSTRUAL CYCLE

Ovarian follicles are composed of an outer layer of thecal cells and an inner layer of granulosa cells which engulf the oocyte and host an antrum (fig.2). The thecal cells have LH receptors, and produce

androgens (testosterone and androstenedione) in response to LH. The androgens cross the basement membrane to reach the granulosa cells where aromatase transforms them into oestrogens (oestradiol and oestrone respectively). Aromatase is an FSH dependant enzyme and the FSH receptors are located on the granulosa cells.

At the end of the preceding cycle, the drop in oestradiol and progesterone (due to the demise of the corpus luteum) decreases the negative feed-back on FSH and this hormone increases in the blood before menses appear. This increase recruits a cohort of follicles which become sensitive to FSH and start to grow.

During the first week after menses (in a 28 days cycle), FSH continues to increase, the follicles grow intensely and FSH increases the expression of its own receptor and of the LH receptor on the granulosa cells. During this period, the follicles produce relatively small amounts of oestradiol and the circulating concentration of this steroid is relatively constant (fig. 3).

During the second week, the follicles continue to grow and since they have increased their FSH receptors on the granulosa cells their aromatase actively transforms the thecal androgens into oestrogens and the circulating oestradiol levels increase. This increase induces a negative feed-back on FSH which decreases slightly in the blood. The follicle which has the highest number of FSH receptors, the maximal aromatase activity and thus produces the highest concentration of oestradiol is named the dominant follicle and will be selected for ovulation, the others gradually degenerate during a process called atresia. Oestradiol continues to increase (particularly due to the activity of the dominant follicle) and reaches a peak about 72h before ovulation. These high levels of oestradiol induce by positive feed-back, a brisk release of LH and FSH (the LH and FSH peaks, fig. 3).

Follicular rupture (ovulation) occurs about 36h after the LH peak. It is due to the fact that granulosa cells have acquired LH receptors (effect of FSH) and are now responsive to LH. This peptide induces the secretion of enzymes which digest the follicular wall. The initial rise of LH (at the beginning of the peak) is sufficient to allow the granulosa cells to secrete small amounts of progesterone which participate in the mechanism of induction of the LH peak.

Once the oocyte has been expelled from the ruptured follicle, LH induces the secretion of progesterone from the remaining granulosa cells which organise themselves in a new gland called the corpus luteum (a process known as luteinisation). Progesterone and oestradiol increase and reach a plateau around day 22. This induces a negative feed-back on LH and FSH which decrease in the circulation. If implantation does not occur, Human Chorionic Gonadotropin (hCG) is not present, the corpus luteum is not sustained any longer and oestradiol and progesterone decline. This decline induces an increase in FSH which will recruit the follicles for the next cycle. Endometrial bleeding occurs because the progesterone levels have fallen below those required to maintain a secretory endometrium.

THE NORMAL VALUES OF HORMONES DURING THE MENSTRUAL CYCLE

Definitions

The *Early Follicular Phase* starts on the first day of the cycle and ends when oestradiol begins to increase. It is characterised by increasing LH and FSH and constant low levels of oestradiol (Fig. 4).

The *Late Follicular Phase* starts with the increase in oestradiol and ends at its preovulatory peak. It is

characterised by increasing oestradiol and decreasing FSH and LH levels (Fig. 4).

The *Early Luteal Phase* starts on the day of ovulation (the day after the LH peak) and ends when progesterone has reached its plateau. It is characterised by increasing progesterone and decreasing LH and FSH levels (Fig. 4).

The *Mid Luteal Phase* corresponds to plateauing progesterone levels. It is characterised by constant elevated progesterone and constant low levels of LH and FSH (Fig. 4).

The *Late Luteal Phase* starts when progesterone decreases and ends on the day preceding the next menses. It is characterised by decreasing progesterone and increasing LH and FSH levels (Fig. 4).

Volunteers and Method

Our study included 20 normal healthy women aged 20 to 35 who have not been taking oral contraceptives for at least 3 months before the start of the study. Daily morning blood samples (10ml) were taken on heparin starting on the first day of their menses and continued to the first day of their next menses. After centrifugation, the plasma samples were aliquoted and stored at -20º C until assayed. Starting on day 10, three urine samples per day (morning, afternoon, evening) were also obtained and urine collection continued until the day after the LH peak. Urinary LH was measured daily to determine the LH peak.

For each volunteer, 3 vaginal ultrasound scans were performed according to the following schedule: day 10, day 13 and two days after the LH peak. A cycle was declared as ovulatory if the dimensions of the corpus luteum as measured 2 days after the LH peak were smaller than the dimensions of the dominant follicle as measured on day 13. All 20 cycles were ovulatory according to this criteria.

LH, FSH, oestradiol and progesterone were measured on Kryptor and statistical evaluation of the results was performed on a Macintosh computer using the Statview program from Abascus.

Results

Concentrations of pituitary gonadotropins and ovarian steroids stratified by functional phases are presented in figure 4 and in tables I to VI. The functional periods of the cycle as defined above are compared to the days of the cycle either calculated from the day of the LH peak or estimated for a 28 and a 35 days cycle. The distribution of the observed values is given by the concentration of each hormone at the 2.5th, 50th (median) and 97.5th percentile. By definition, 95% of the normal population is between the 2.5th and the 97.5th percentiles of the distridution.

Table I: FSH values in IU/l during the functional periods of thecycle

Period	Days	Days	Days	Mean	2.5th Centile	50th Centile	97.5th Centile
	From LH	28 days Cycle	35 days Cycle			Median	
Early Foll.	-15 to -5	1-9	1-15	5.59	2.33	5.64	8.88
Late Foll	-4 to 0	10-14	16-20	4.09	1.21	3.97	7.71

Ealy Lut.	1-3	15-17	21-23	5.20	1.76	4.60	13.32
Mid Lut.	4-9	18-23	24-29	2.71	0.78	2.59	6.15
Late Lut	10-15	24-29	30-35	2.48	0.20	2.31	7.52

Table II: LH values in IU/l during the functional periods of the cycle

Period	**Days**	**Days**	**Days**	**Mean**	**2.5th Centile**	**50th Centile**	**97.5th Centile**
	From LH	28 days Cycle	35 days Cycle			Median	
Early Foll.	-15 to -5	1-9	1-15	3.40	1.12	3.25	5.90
Late Foll	-4 to 0	10-14	16-20	5.65	2.34	4.43	16.11
Ealy Lut.	1-3	15-17	21-23	7.00	1.91	6.03	17.30
Mid Lut.	4-9	18-23	24-29	3.64	0.73	3.12	8.56
Late Lut	10-15	24-29	30-35	2.77	0.59	2.40	7.51

Table III: Oestradiol values in pg/ml during the functional periods of the cycle

Period	**Days**	**Days**	**Days**	**Mean**	**2.5th Centile**	**50th Centile**	**97.5th Centile**
	From LH	28 days Cycle	35 days Cycle			Median	
Early Foll.	-15 to -5	1-9	1-15	57.6	11.7	48.5	167.2
Late Foll	-4 to 0	10-14	16-20	196.3	31.8	167.7	559.1
Ealy Lut.	1-3	15-17	21-23	129.0	31.5	120.9	294.0
Mid Lut.	4-9	18-23	24-29	203.5	58.3	211.6	342.3
Late Lut	10-15	24-29	30-35	132.8	16.1	118.7	347.4

Table IV: Oestradiol values in pmol/l during the functional periods of the cycle

Period	**Days**	**Days**	**Days**	**Mean**	**2.5th Centile**	**50th Centile**	**97.5th Centile**
	From LH	28 days Cycle	35 days Cycle			Median	

Early Foll.	-15 to -5	1-9	1-15	211.4	42.9	178.0	613.6
Late Foll	-4 to 0	10-14	16-20	720.4	116.7	615.5	2051.9
Ealy Lut.	1-3	15-17	21-23	473.4	115.6	443.7	1079.0
Mid Lut.	4-9	18-23	24-29	746.9	214.0	776.6	1256.2
Late Lut	10-15	24-29	30-35	487.4	59.1	435.6	1275.0

Table V: Progesterone values in ng/ml during the functional periods of the cycle

Period	**Days**	**Days**	**Days**	**Mean**	**2.5th Centile**	**50th Centile**	**97.5th Centile**
	From LH	28 days Cycle	35 days Cycle			Median	
Early Foll.	-15 to -5	1-9	1-15	0.58	0.05	0.49	1.64
Late Foll	-4 to 0	10-14	16-20	0.50	0.02	0.44	1.34
Ealy Lut.	1-3	15-17	21-23	4.49	0.81	4.00	10.82
Mid Lut.	4-9	18-23	24-29	11.09	6.60	11.07	16.90
Late Lut	10-15	24-29	30-35	5.38	0.51	4.47	14.61

Table VI: Progesterone values in nmol/l during the functional periods of the cycle

Period	**Days**	**Days**	**Days**	**Mean**	**2.5th Centile**	**50th Centile**	**97.5th Centile**
	From LH	28 days Cycle	35 days Cycle			Median	
Early Foll.	-15 to -5	1-9	1-15	1.84	0.16	1.56	5.22
Late Foll	-4 to 0	10-14	16-20	1.59	0.06	1.40	4.26
Ealy Lut.	1-3	15-17	21-23	14.28	2.58	12.72	34.41
Mid Lut.	4-9	18-23	24-29	35.27	21.00	35.20	53.74
Late Lut	10-15	24-29	30-35	17.11	1.62	14.21	46.46

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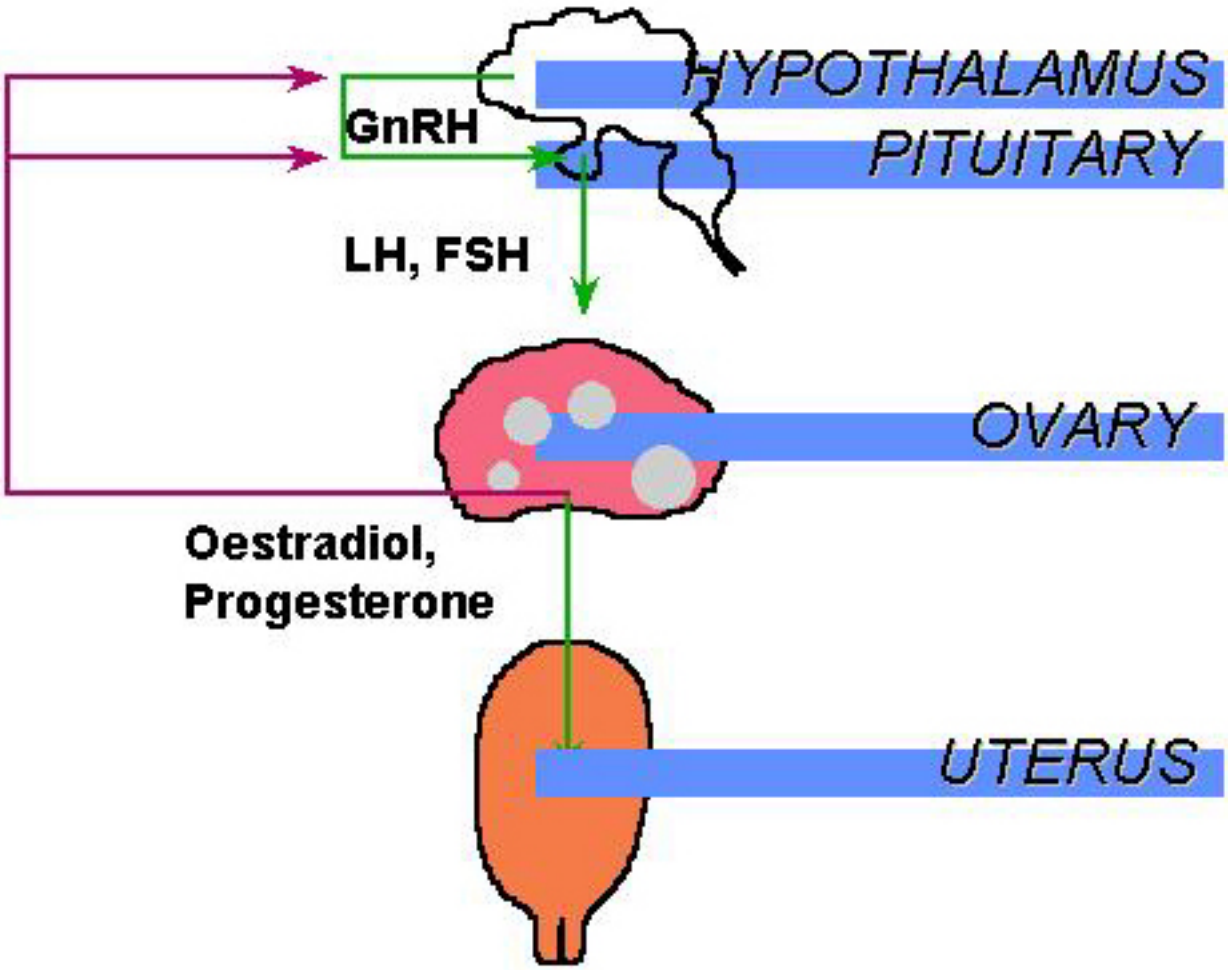
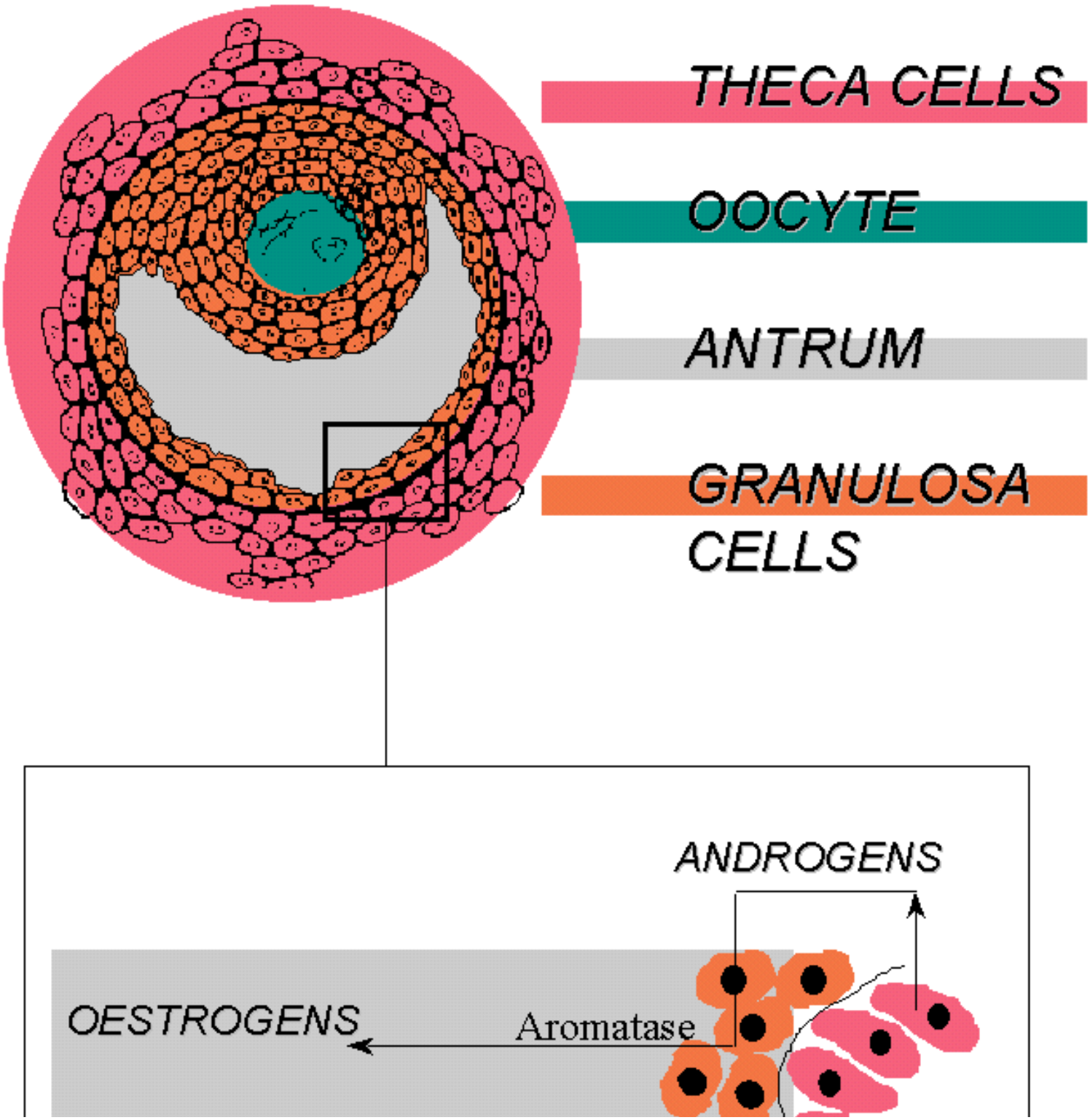
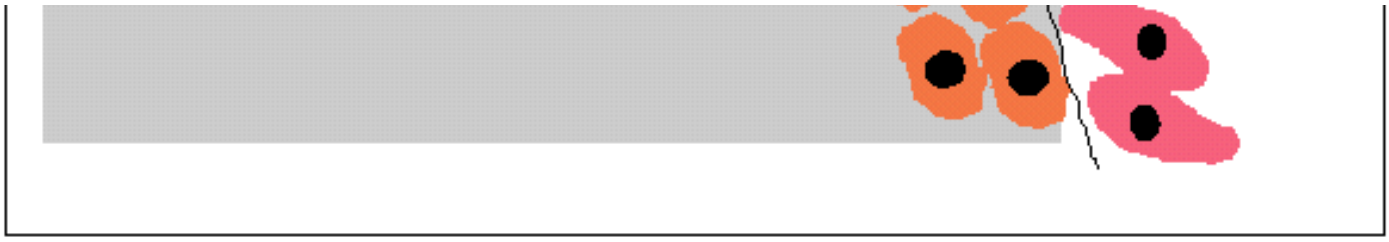
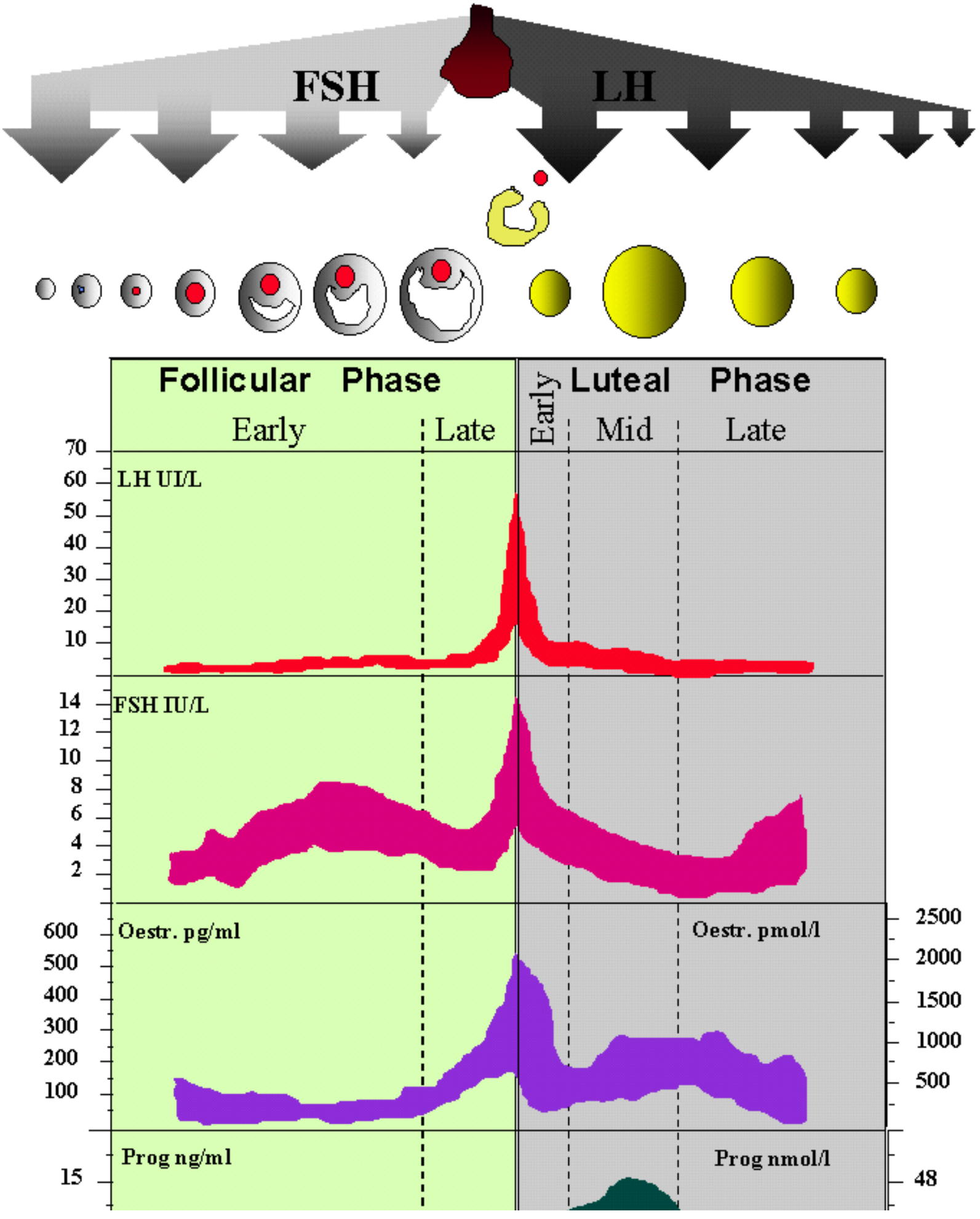
THE MENSTRUAL CYCLE



THE OVARIAN FOLLICLE






FSH
LH
Follicular Phase
Early
Late
Luteal Phase
Early
Mid
Late
LH UI/L
70
60
50
40
30
20
10
FSH IU/L
14
12
10
8
6
4
2
Oestr. pg/ml
600
500
400
300
200
100
Oestr. pmol/l
2500
2000
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1000
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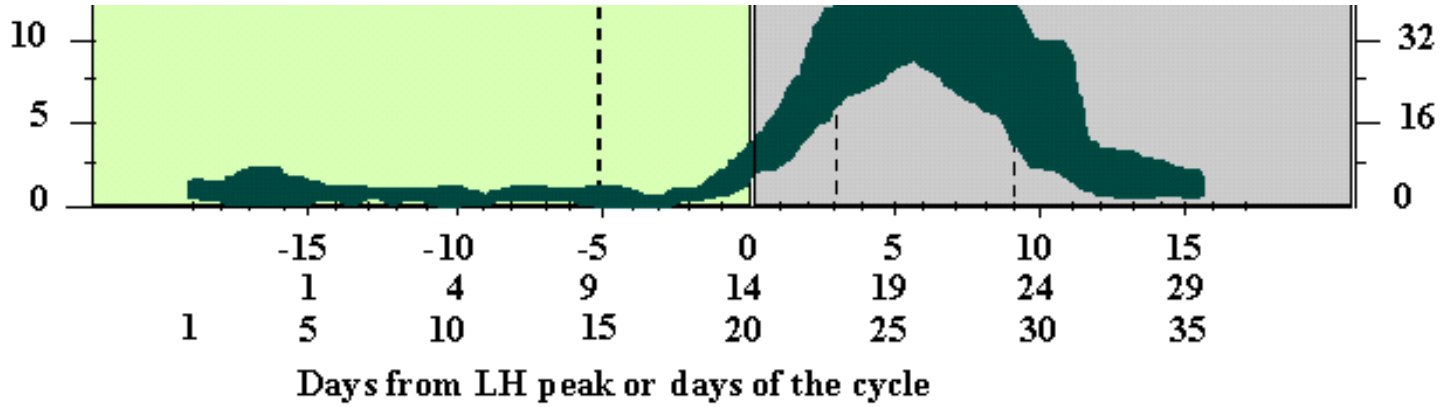
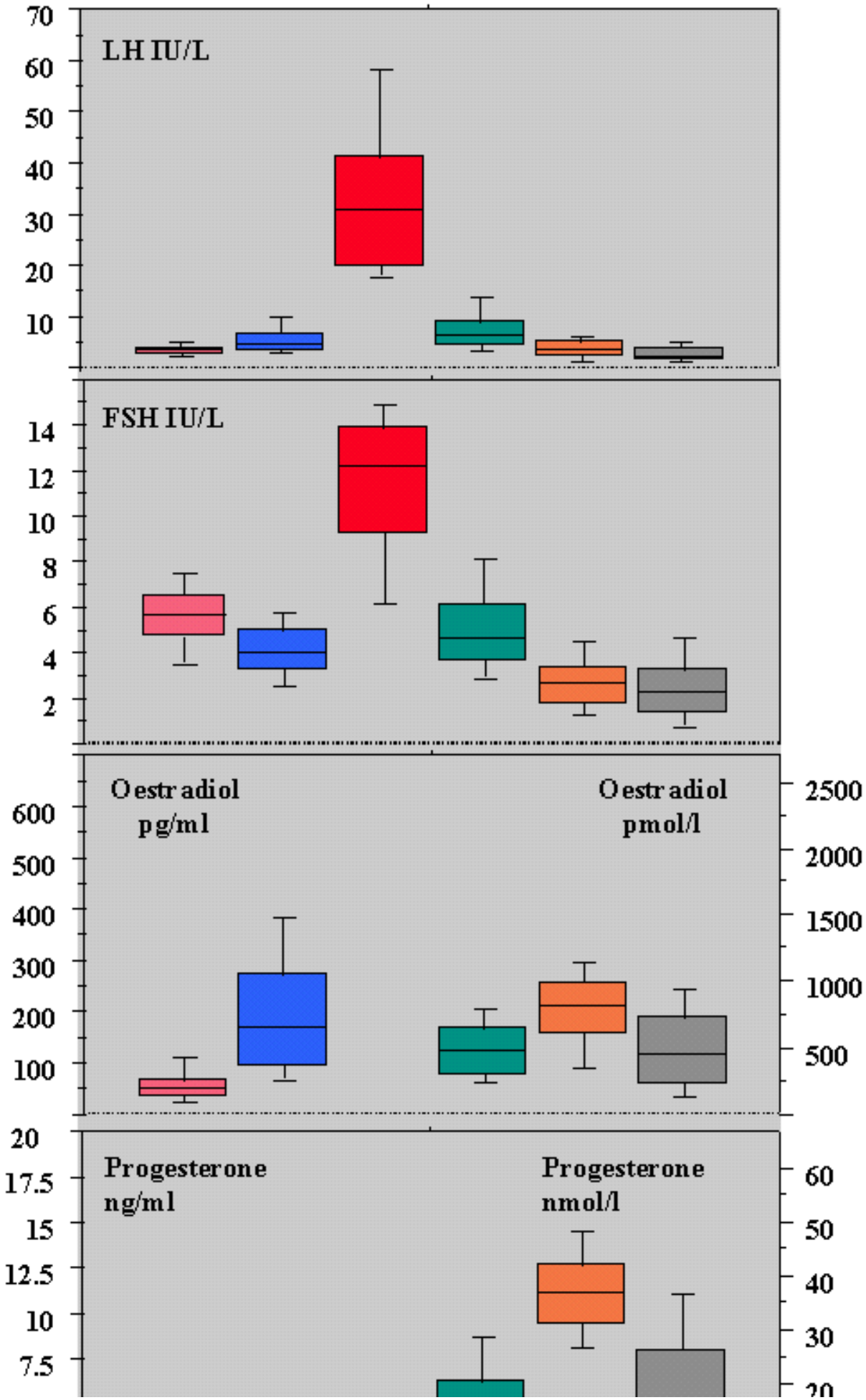
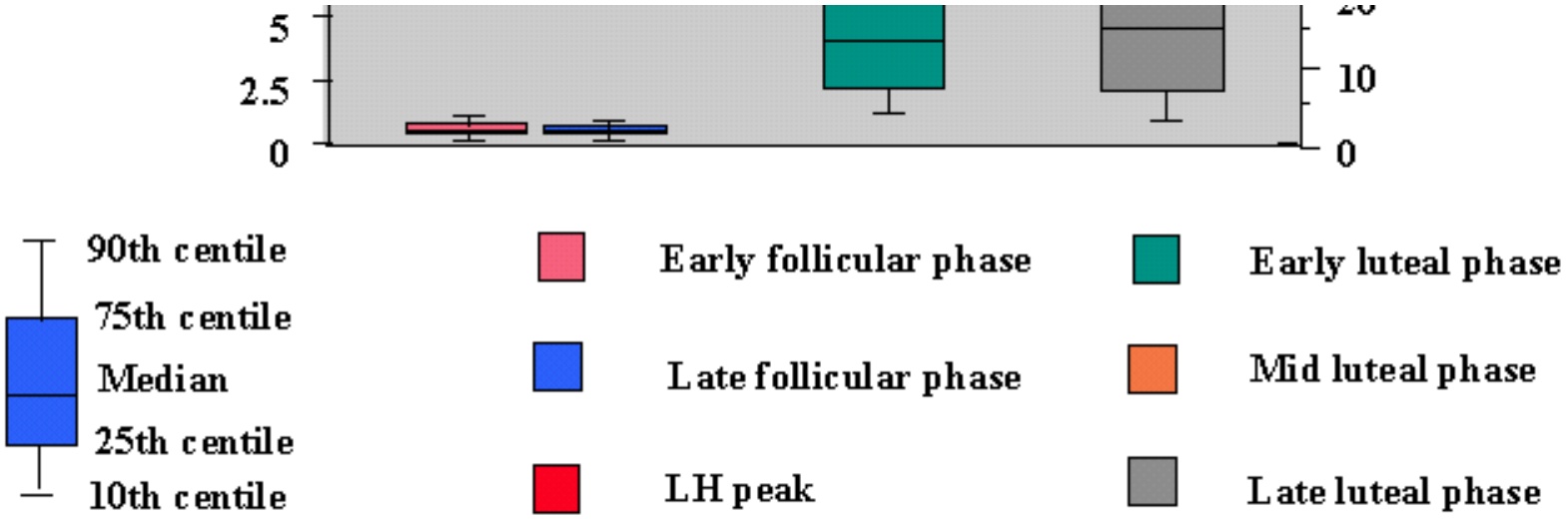
Prog ng/ml
15
Prog nmol/l
48


10
5
0
32
16
0
-15
-10
-5
0
5
10
15
1
4
9
14
19
24
29
1
5
10
15
20
25
30
35
Days from LH peak or days of the cycle


LH IU/L
70
60
50
40
30
20
10
FSH IU/L
14
12
10
8
6
4
2
Oestradiol pg/ml
600
500
400
300
200
100
Oestradiol pmol/l
2500
2000
1500
1000
500
Progesterone ng/ml
20
17.5
15
12.5
10
7.5
Progesterone nmol/l
60
50
40
30
20


5
2.5
0
10
0
90th centile
75th centile
Median
25th centile
10th centile
Early follicular phase
Late follicular phase
LH peak
Early luteal phase
Mid luteal phase
Late luteal phase