

Gonadotropins in the Infant Chimpanzee: A Sex Difference (37718)

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We have reported that serum gonadotropin levels, especially those of follicle-stimulating hormone (FSH), are higher in girls than in boys during infancy (1). In addition, there is substantial intersubject variation in individual FSH values in girls less than 2 years of age, whereas the range of values in boys is relatively small (1). We wondered whether cyclic variations in hormone secretion might explain this wide scatter in FSH values in infant girls. Serial blood sampling from healthy human infants is ethically unacceptable. Since chimpanzee gonadotropins cross-react in parallel fashion with human gonadotropin standards in radioimmunoassay systems for human FSH and luteinizing hormone (LH) (2), and the chimpanzee appears to resemble man with respect to adult menstrual function (2, 3), the question of cyclicity of gonadotropin secretion was studied in infant chimpanzees. Preliminary findings have been reported (4).

Materials and Methods. Five female and four male chimpanzees ranging in age from 0.4 to 2.0 years were studied. All were born and raised at the International Center for Environmental Safety (previously Holloman Air Force Base Colony). Studies were carried out between November–December 1970 (Animal Nos. 709, 710, 713, 714) and March–May 1972 (Animal Nos. 767, 763, 754, 755, 756). Lights were kept on from 0700 to 1700 hr. Three to five milliliters of peripheral venous blood were obtained under manual

restraint at 0730 hr at 1–3-day intervals for 25–40 days. A few additional samples were obtained at other times of day. The sera were stored at -20° until analyzed in a single assay run for each study for FSH (5) in duplicate and for LH (6) in single samples or in duplicate when sufficient serum was available. Data are expressed in terms of the human pituitary standard LER-907. The coefficient of variation of duplicate determinations for individual animals averaged 8% (range 4–16%) for FSH and in two animals was 15 and 16% for LH.

Results. Individual values for serum FSH and LH are shown in Figs. 1 and 2, respectively. Statistical analysis of these data is shown in Table I. The overall mean level of FSH in the females was significantly higher than that in the males. There was no significant sex difference in the mean levels of LH. The day-to-day variability for both FSH and LH levels was significantly greater in females than in males. There was no apparent age or seasonal effect on individual mean levels or degree of variability.

Most, if not all, of the variability of FSH levels in the males and LH levels in both sexes was accounted for by variability between duplicate values (Figs. 1 and 2). This was clearly not the case for FSH levels in the females which, in addition, appeared to show periodic variation. Accordingly, the FSH levels in the females were further analyzed for the presence of day-to-day cyclicity by means of a cosine function computer program (Table II). Statistically significant ($p < 0.05$) sine-wave cycles which accounted for 30–69% of the variability could be fitted to each of the female's values.

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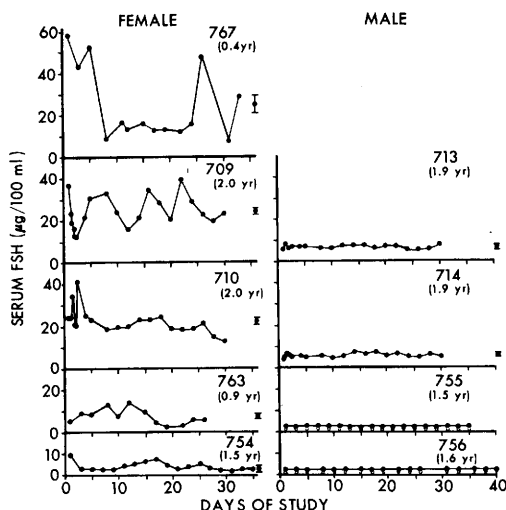


FIG. 1. Serial levels of serum FSH in female and male infant chimpanzees expressed as μg LER-907 standard/100 ml. Numbers in each panel refer to animal number and age in years. v refers to values below the limit of sensitivity of the assay. I represents the 95% confidence limits about any individual measurement, calculated according to the method of Chebib and Burdick (7).

The cycle periods ranged from 8.3 to 25.0 days.

Discussion. Thus, in the infant chimpanzee as in the infant human (1), FSH levels are higher in the female than in the male. The highest values of FSH in the female infants are comparable to those seen during the adult chimpanzee menstrual cycle where peak values are in the 30–50 $\mu\text{g}/100$ ml range (2). The failure to find a sex difference in

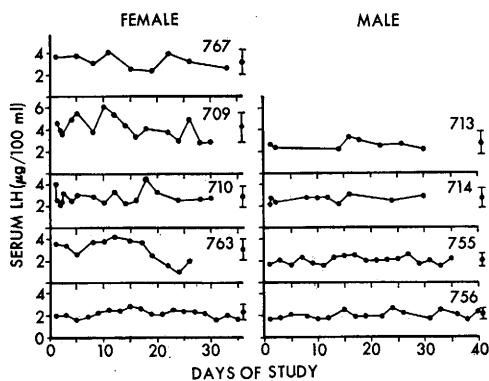


FIG. 2. Serial levels of serum LH in female and male infant chimpanzees expressed as μg LER-907 standard/100 ml. Symbols are as for Fig. 1.

TABLE I. Statistical Analysis of Differences Between Sexes for Level and Variability of Serum FSH and LH Levels.

Serum level	Statistic	Female								Male				Sex difference	p^a
		767	709	710	763	754	Pooled	713	714	755	756	Pooled			
FSH	<i>n</i>	14	20	20	12	18	—	20	20	18	17	—	—	—	—
	Mean	24.8	24.2	22.4	7.4	3.9	16.54	6.8	5.9	1.0 ^b	1.0 ^b	3.68	—	<0.001	
	Variance	317.3	57.1	39.9	13.5	4.9	78.4	0.6	0.6	1.1 ^b	1.1 ^b	0.8	—	<0.001	
LH	Coefficient of variation (%)	72	31	28	50	57	54	12	14	100	100	25 ^b	—	—	
	<i>n</i>	9	17	17	12	18	—	8	10	18	17	—	—	—	
	Mean	3.3	4.2	2.9	3.0	2.2	3.12	2.7	2.7	2.0	2.0	2.35	—	>0.1	
LH	Variance	0.4	0.9	0.4	1.1	0.1	0.6	0.1	0.1	0.1	0.1	0.1	—	<0.001	
	Coefficient of variation (%)	19	23	23	34	16	24	14	12	16	14	14	—	—	

^a Differences between mean levels assessed by *t* test for samples with unequal variances (8). Differences between pooled variances assessed by variance ratio (9).

^b All levels undetectable (<2 $\mu\text{g}/100$ ml). In order to avoid error when assessing sex difference in variance, variability was maximized by arbitrarily assigning values of 2 and 0 to alternate samples.

TABLE II. Presence of Day-to-Day Sine-Wave Cyclicity of Serum FSH Levels in Individual Female Subjects.^a

Subject	Period (days)	Level	Amplitude	% Variability due to cyclicity (r^2)	p^*
767	25.0	22.7 ± 4.0	15.7 ± 5.6	42	0.049
709	8.3	26.6 ± 1.5	7.3 ± 2.2	46	0.002
710	17.2	21.5 ± 1.3	4.4 ± 1.9	30	0.047
763	23.8	7.6 ± 0.7	4.4 ± 0.9	69	0.005
754	22.8	4.2 ± 0.5	2.0 ± 0.6	38	0.026

^a The computer program performs several cycles of least-squares fitting of the data to a cosine function, incrementing the period in each cycle, and successively reducing the increment around the point of best fit. The level, amplitude, and phase and their standard errors are calculated for the optimum period according to the formulae of Halberg *et al.* (10).

* Probability that % variability due to cyclicity equals 0.

mean LH levels in the chimpanzee, whereas levels are higher in human female infants (1), may simply reflect the smaller number of chimpanzees studied. It has recently been reported that in the rat, serum FSH and LH levels are also higher in newborn females, reaching concentrations above the adult diestrus range (11). These higher gonadotropin levels in females may be due to relative refractoriness of the ovary to gonadotropin stimulation (11).

The additional finding in the present study of apparent rhythmic fluctuation of serum FSH levels (and perhaps to a lesser extent of serum LH levels) in female but not in male infants is reminiscent of a similar pattern we have observed in early pubertal (premenarcheal) girls, in which the cycle periodicity appears to vary from subject to subject (12). In contrast, FSH levels in the preadolescent girl are low, and rhythmic fluctuations are not seen (12). Thus, it appears that rhythmic secretion of FSH is a sex-specific characteristic of the female primate which is present in infancy, lost or damped during childhood years, and reappears some years prior to the menarche (12). It is tempting to speculate that this characteristic of gonadotropin regulation may be the result of hypothalamic patterning conditioned by a sex difference in prenatal exposure to endogenous androgen (13) and may have an anatomic correlate in the sexual dimorphism present in the preoptic area of the rat brain (14).

Summary. Serial circulating levels of FSH were higher in five female than in four male infant (0.4–2.0 years) chimpanzees. A rhythm in FSH levels was observed in the females with a periodicity of 8–25 days. There was no sex difference in mean LH levels. However, greater day-to-day variability was observed in the females.

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