

## EFFECTS OF LH-RH ON SERUM GONADOTROPINS IN CHILDREN AND ADOLESCENTS

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### SUMMARY

Readily releasable stores of pituitary gonadotropins can be evaluated by radioimmunoassay of serum LH and FSH after injection of LH-RH in either prepubertal or pubertal children. The data summarized here are obtained from 200 normal or agonadal children or adolescents with precocious or delayed puberty, hypopituitarism or undescended testes. They are injected with 0.1 mg/m<sup>2</sup> LH-RH, blood being collected from — 15 to 90 minutes. It is concluded that :

- Prepubertal children respond to LH-RH.
- Increase of LH stores is age-related and may begin in the late prepubertal stage in both sexes as a distinctive feature of hypothalamo-pituitary prepubertal maturation.
- Maturation of FSH stores, both age and sex-related, accounts for main variations of pubertal pattern in boys and girls.

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Readily releasable stores of pituitary gonadotropins can be evaluated by radioimmunoassay of serum LH and FSH after injection of synthetic luteinizing hormone-releasing hormone (LH-RH) in either prepubertal or pubertal children. Their evaluation contributes to an understanding of human pubertal pituitary changes and hypophysogonadal disorders in children and adolescents.

The data summarized here were obtained before and after intravenous injection of 0.1 mg/m<sup>2</sup> of LH-RH, blood being collected from — 15 to 90 minutes. Standards and antisera, generously provided by the NIH, were used for radioimmunoassay : LER 960 for LH, LER 1366 for FSH. Only mean basal and peak values and/or post-stimulatory increase ( $\Delta$ ) will be discussed.

## NORMAL SUBJECTS

LH increase elicited by LH-RH is constant in prepubertal boys and girls, and usually maximal 20 to 30 minutes after venous injection of releasing hormone. FSH increase begins later, maximal level being reached after 30 to 90 minutes. It is constant in girls but not in boys.

Three groups of normal subjects have been studied (fig. 1 and 2) : group A (< 1), 9 boys and 9 girls 1 to 12 months old ; group B (Pre), 13 prepubertal boys and 12 prepubertal girls more than 12 months old ; group C (Pub), 10 males and 11 females having reached partial or complete pubertal maturation.

In boys (fig. 1), LH response decreases slightly after 1 year and increases significantly ( $p < 0.01$ ) at the onset of puberty. The FSH response rises with age,  $\Delta$  FSH increase being insignificant from group A to B, and significant ( $p \leq 0.01$ ) at the onset of puberty (JOB *et al.*, 1972 ; GARNIER *et al.*, 1974).

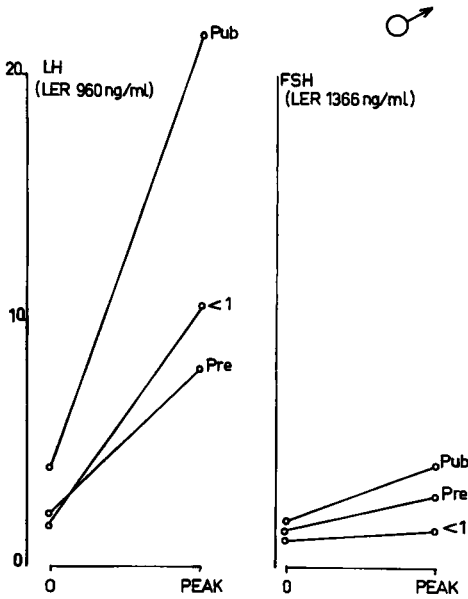


FIG. 1. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in normal boys

< 1 : 1 to 12 months old  
Pre : prepubertal boys  
Pub : pubertal boys

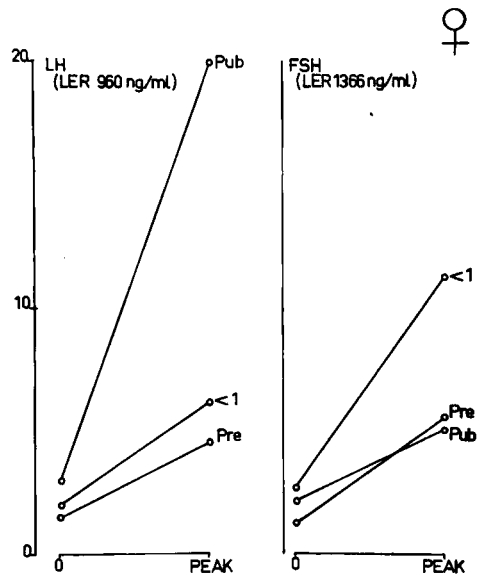


FIG. 2. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in normal girls

< 1 : 1 to 12 months old  
Pre : prepubertal girls  
Pub : pubertal girls

In girls (fig. 2), the variation of LH response with age is similar to that in boys. A striking feature is the high FSH releasable store in infant girls, significantly reducing with age from infancy to childhood ( $p \leq 0.05$ ) and from childhood to puberty ( $p \leq 0.05$ ) (JOB *et al.*, 1972 ; GARNIER *et al.*, 1974).

Comparison between males and females (table I) shows no significant difference in pituitary LH reserve, which increases similarly in both sexes at the onset of puberty. But FSH reserve is significantly ( $p \leq 0.01$ ) higher in female than in male infants and prepubertal children, and shows inverse trends, increasing with age in males and decreasing from infancy to puberty in females. A « late prepubertal » stage can be identified in both sexes, according to GRUMBACH *et al.*, by the increase of mobilizable LH reserve in the year preceding the onset of some clinical development of secondary sex characteristics (GARNIER *et al.*, 1974).

TABLE I

*Increase ( $\Delta$ ) from basal to peak levels of serum gonadotropins in normal subjects*

	LH (LER 960 ng/ml)		FSH (LER 1366 ng/ml)	
	Males	Females	Males	Females
<i>Group A</i>				
Infants 1 to 12 months old	8.96 (N.S.)	<i>(0.05)</i> 4.08 (N.S.)	0.26 (0.05)	<i>(0.01)</i> 8.32 (0.05)
<i>Group B</i>				
Prepubertal children more than 12 months old	5.91 (0.01)	(N.S.) 3.06 (0.01)	1.47 (N.S.)	<i>(0.01)</i> 4.36 (0.05)
<i>Group C</i>				
Pubertal adolescents and adults	17.64	(N.S.) 17.00	2.24	(N.S.) 2.87

Italics in brackets : significance of differences.

These data in normal children and adolescents may be summarized as follows :

- 1) Prepubertal children respond to LH-RH.
- 2) Age-related and sex-related variations of this response are more significant than variations of basal levels of LH and FSH.
- 3) Age-related variation of  $\Delta$  LH is the same in both sexes ;
- 4) Age-related variation of  $\Delta$  FSH in girls is opposite to that in boys. This fact may be related to perinatal imprinting of human hypothalamus (improbable) ; or to different negative feedback by prepubertal testes and ovaries (probable).

#### AGONADAL PATIENTS

Complementary data are given by LH-RH test in agonadal children and adolescents, either with complete congenital gonadal dysgenesis or with acquired accidental or surgical castration. We have studied 25 cases of agonadism between 1 month

and 18 years of age (fig. 3). FSH reserve increased more than LH reserve. Patients 12 years or older ( $A_2$ ) had significantly ( $p \leq 0.01$ ) higher pituitary gonadotropic stores than patients under 12 years ( $A_1$ ). Among these, mobilizable gonadotropic stores were higher in the 0 to 7 year group than in the 7 to 11 year subjects. These data led to the following physiologically significant conclusions (JOB *et al.*, 1974 b) :

- 1) Prepubertal gonads have more negative feedback effect on FSH secretion than on LH secretion ;
- 2) In the absence of gonads, a reduction of pituitary gonadotropic stores occurs from 8 to 11 years, thus suggesting a negative feedback effect of adrenal steroids.
- 3) The age-related pituitary gonadotropic spurt begins at 12 years and is not related to the effect of gonadal secretions.

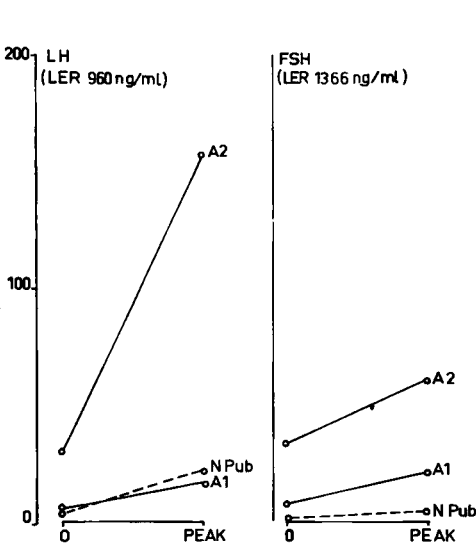


FIG. 3. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in gonadal children

N Pub : normal pubertal children  
 $A_1$  : children 12 years old  
 $A_2$  : children 12 years old

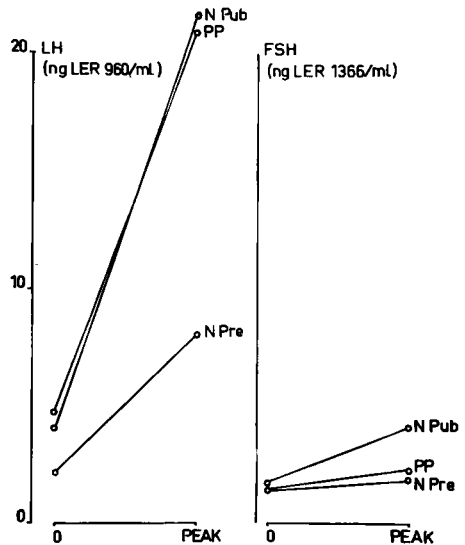


FIG. 4. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in boys with precocious puberty

N Pre : normal prepubertal boys  
 N Pub : normal pubertal boys  
 PP : precocious pubertal boys

### CHRONOLOGIC VARIATIONS OF THE ONSET OF PUBERTY

Twenty cases of central precocious puberty have been studied in 5 boys (fig. 4) and 15 girls (fig. 5). In both sexes, LH stores were similar to those in normal puberty, and FSH stores differed slightly but not significantly from normal. So, it can be stated that whether the primary hypothalamic pubertal change is physiological or related to some central disturbance, it leads to similar maturation of pituitary gonadotropic secretion (JOB *et al.*, 1973).

Premature thelarche is a variation of normal puberty in girls : isolated development of breast between 2 to 6 years, followed by normal puberty at 10-12 years. Our data on 12 girls with isolated premature thelarche (PT) showed releasable LH and FSH pituitary stores similar to those observed in normal infant girls less than 1 year old (fig. 6). Hence, we hypothesized that premature thelarche is correlated with sustained persistence of the high FSH reserve observed in normal female infants (JOB *et al.*, 1973).

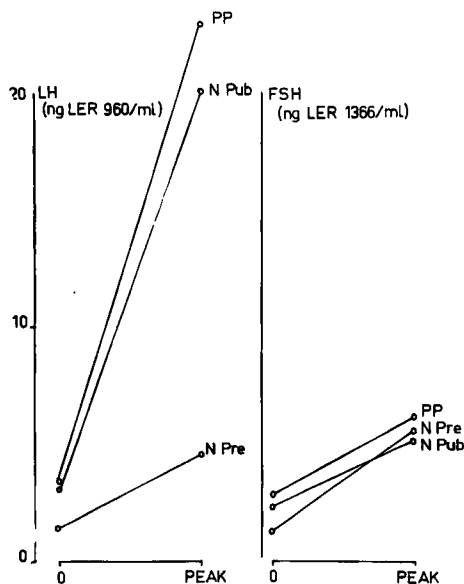


FIG. 5. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in girls with precocious puberty

N Pre : normal prepubertal girls  
N Pub : normal pubertal girls  
PP : precocious pubertal girls

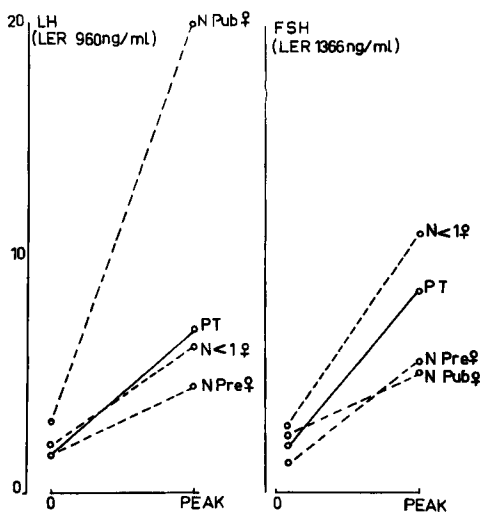


FIG. 6. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in girls with premature thelarche

N 1 : normal infant girls 1 year  
N Pre : normal prepubertal girls  
N Pub : normal pubertal girls  
PT : girls with premature thelarche

We studied 20 cases of constitutionally delayed puberty in prepubertal males aged 15 to 18 years who later presented normal onset of puberty. Mean LH reserve in this group was significantly higher than in normal prepubertal boys, and did not differ significantly from that in pubertal males (fig. 7 DA). FSH reserve was in the prepubertal range. These findings were similar to those obtained in normal late prepubertal boys. They confirm that a definite increase of LH pituitary reserve precedes the clinical onset of puberty, and suggest that low FSH stores can prevent this onset despite relatively high LH stores.

Data obtained with LH-RH in precocious and delayed puberty allow the following conclusions :

1. Chronological variations of puberty do not alter the sequence of events leading to full gonadotropic maturation ;
2. Higher frequency of delayed puberty in boys and precocious puberty in girls correlates to the male and female patterns of  $\Delta$  FSH maturation.

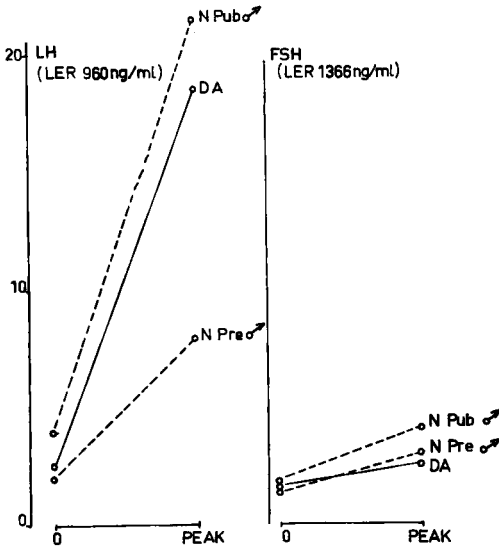


FIG 7. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in boys with delayed puberty

N Pre : normal prepubertal boys  
 N Pub : normal pubertal boys  
 DA : boys with delayed puberty

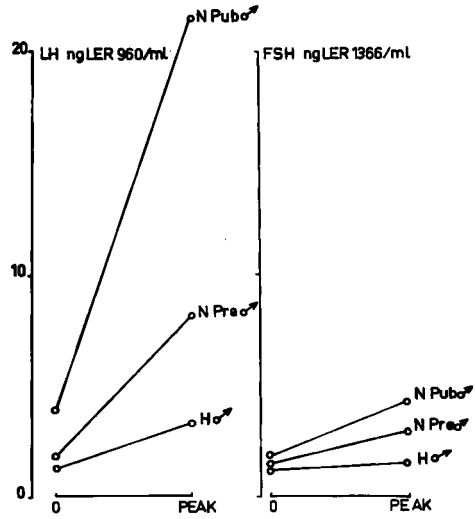


FIG. 8. — Mean basal (○) and peak levels (Peak) of LH and FSH after injection of LH-RH in hypogonadotropic male patients

(H ♂ compared with normal pubertal or prepubertal children)

HYPOPITUITARISM AND CRYPTORCHIDISM

Response to LH-RH has been extensively studied in adult cases of hypogonadotropic hypogonadism, and has evidenced wide heterogeneity : absent or blunted response in most patients, response in the normal range in some. We studied 5 cases of clinically documented hypogonadotropism with complete lack of puberty but with bone age corresponding to the pubertal onset ( $\leq 14$  years) (fig. 8 H), and 20 cases of pituitary dwarfism in children with bone age up to 11 years so that hypogonado-

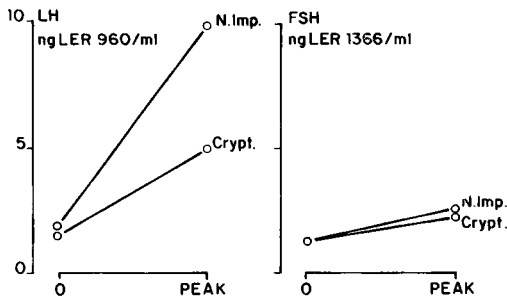


FIG. 9. — Mean basal (○) and peak levels (PEAK) of LH and FSH after injection of LH-RH in cryptorchid boys

N imp : normal impubertal boys  
 Crypt : cryptorchid boys

tropism could be suspected but not proven. Though some individuals demonstrated a borderline response to LH-RH, mean  $\Delta$  LH and  $\Delta$  FSH in these two groups were significantly ( $p \leq 0.01$ ) subnormal. Furthermore, they were significantly ( $p \leq 0.01$ ) lower than in adolescents with constitutional delay of puberty; this point has diagnostic significance (CHAUSSAIN *et al.*, 1974).

In a group of 39 prepubertal boys with uni or bilaterally undescended testes (fig. 9, crypt.), mean LH response to LH-RH was found to be significantly ( $p \leq 0.01$ ) lower than in a control group, while FSH response was the same in the two groups. This may correlate with a delay of LH secretion in some boys with undescended testes and/or inclusion of hypogonadotropic patients among these prepubertal individuals (JOB *et al.*, 1974 a).

### CONCLUSION

In summarizing the main conclusions drawn from these data, it may be stated that :

1. Study of LH-RH-mobilizable pituitary reserve in humans amplifies the data obtained by assay of plasma gonadotropins and offers a valuable tool for assessment of gonadotropic status in clinical cases.
2. Increase of LH stores is age-related and may begin in the late prepubertal stage as a distinctive feature of hypothalamo-pituitary prepubertal maturation.
3. Maturation of FSH stores, both age and sex-related, accounts for main variations of pubertal pattern in boys and girls.

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### RÉSUMÉ

#### EFFETS DU LH-RH SUR LES GONADOTROPINES PLASMATIQUES CHEZ LES ENFANTS ET ADOLESCENTS

Les contenus hypophysaires mobilisables en FSH et LH peuvent être estimés par dosage radioimmunologique de ces hormones dans le plasma sanguin après injection de LH-RH à des enfants impubères ou pubères. Les données rapportées ici concernent 200 enfants ou adolescents, soit normaux, soit agonadiques, soit insuffisants hypophysaires, soit avec des testicules non descendus, soit avec une puberté précoce ou retardée. Ils ont reçu une injection de 0,1 mg/m<sup>2</sup> de LH-RH, le sang étant collecté de — 15 à 90 minutes.

Les données recueillies ont permis d'établir que :

- les enfants impubères répondent à LH-RH,
- l'augmentation de LH mobilisable est liée à l'âge et peut commencer vers la fin du stade prépubère dans les deux sexes. Elle constitue un signe distinctif de la maturation prépubère du système hypothalamo-hypophysaire.
- les variations de FSH mobilisable sont liées à l'âge mais inverses dans les deux sexes.

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