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PITUITARY RESPONSIVENESS TO LHRH AND TRH IN ADOLESCENT GIRLS

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Summary

Puberty is characterized by a progressive maturation of the hypothalamus-pituitary gonadal axis which, in girls, results in menarche. The first menstrual cycles are usually irregular and anovulatory, and the subtle positive and negative regulation of sex steroids on the hypothalamus-pituitary axis has probably not reached adult maturity. An investigation has been carried out in 99 normal adolescent girls, divided into 3 groups: 1-2, 3-4 and 5 years after menarche, by measuring basal hormonal values as well as the responses to LHRH and TRH during the follicular and luteal phases.

Basal FSH and LH values reached adult levels after the second year of menarche, while FSH and LH responses to 50 µg LHRH showed a regular and progressive increase from 1 to 5 years post-menarche, resulting, in the 5-year group and in spite of the half dose received, in definitely higher FSH and LH responses than those observed in the adult women after 100 µg LHRH. This enhanced pituitary responsiveness to LHRH is due to still progressively increasing estradiol and progesterone secretions, the latter hormone remaining still lower than in the adults. Basal prolactin levels were significantly higher than those found in adult women with a slightly increased prolactin response to TRH and an exaggerated one of TSH, with normal T_3 and T_4 levels.

These data show that from the onset of menarche to the complex and subtle adult menstrual cycle regulation, there is a continuing maturation of the hypothalamus-pituitary axis of the gonads which lasts approximately 5 years. It is characterized by increasing E_2 secretion, low progesterone secretion and slightly increased prolactin levels, with a frequently impaired luteal phase. The enhanced pituitary sensitivity to releasing hormones is due to the positive feedback mechanism of E_2 which is not yet associated with adequate progesterone se-

cretion for a negative feedback, as in adult women. Thus, adolescence is still a maturation period, the onset of ovulation being the final step in this development.

Résumé

La puberté est caractérisée par la maturation progressive de l'axe hypothalamo-hypophysaire des gonades qui, chez les jeunes filles, aboutit à la ménarque. Les premiers cycles menstruels sont habituellement irréguliers et anovulatoires et le rétro-contrôle subtil positif et négatif des stéroïdes sexuels sur l'axe hypothalamo-hypophysaire n'a probablement pas atteint la maturité de l'adulte. 99 adolescentes réparties en trois groupes: 1-3, 3-4 et 5 ans après l'apparition de la ménarque ont été examinées. Les valeurs de base des hormones hypophysaires et les réponses au LHRH et au TRH ont été mesurées au cours des phases folliculaires et lutéales. Les valeurs de base de FSH et de LH atteignent les taux des adultes après la deuxième année. Les réponses des gonadotrophines à 50 µg de LHRH montrent une augmentation régulière et progressive de 1 à 5 ans, aboutissant dans le groupe de "5 ans" à des réponses de FSH et de LH nettement plus élevées que celles qui sont observées chez les femmes adultes, malgré les demi-doses administrées (50 vs. 100 µg). Cette sensibilité augmentée de l'hypophyse au LHRH est due aux sécrétions d'oestradiol et de progestérone qui augmentent progressivement, la progestérone restant cependant plus basse que chez les adultes. Les taux basaux de prolactine sont significativement plus hauts que ceux des femmes adultes, avec une réponse de la prolactine au TRH légèrement augmentée, une réponse de la TSH exagérée et des taux de T_3 et T_4 normaux. Ces données montrent que, dès l'apparition de la ménarque jusqu'à la régulation subtile et complexe du cycle menstruel adulte, il y a une maturation constante de l'axe hypothalamo-hypophysaire des gonades qui dure environ 5 ans. Elle est caractérisée par une sécrétion de E_2 croissante, de progestérone encore insuffisante et des taux de prolactine légèrement augmentés, ainsi qu'une fonction lutéale souvent insuffisante.
L'augmentation de la sensibilité hypophysaire aux "releasing hormones" est due au mécanisme de rétro-contrôle positif de l'E_2 qui n'est pas encore associé à une sécrétion de progestérone adéquate pour un rétro-contrôle négatif, comme chez les femmes adultes.
Ainsi l'adolescence est encore une période de maturation, l'apparition de l'ovulation représentant la phase finale de ce développement.

Zusammenfassung

Die Pubertät ist durch die fortschreitende Reifung der hypothalamisch-hypophysär-gonadalen Achse gekennzeichnet, welche beim Mädchen zur Menarche führt.

Die ersten Menstruationszyklen sind im allgemeinen unregelmässig und anovulatorisch, und die subtile positive und negative Steuerung der hypothalamisch-hypophysären Achse durch die Sexualsteroide hat wahrscheinlich noch nicht die Reife des Erwachsenen-Alters erreicht. In der vorliegenden Studie wurden 99 gesunde adoleszente Mädchen untersucht, eingeteilt in 3 Gruppen: 1 bis 2, 3 bis 4 und 5 Jahre nach der Menarche, und zwar wurden basale Hormonwerte ebenso wie die hormonalen Antworten auf LHRH und TRH während der Follikel- und der Corpus luteum-Phase gemessen.

Die basalen FSH- und LH-Spiegel erreichten nach dem zweiten Jahr nach der Menarche Erwachsenen-Werte, während die FSH- und LH-Antworten auf Stimulation mit 50 µg LHRH einen regelmässigen und fortschreitenden Anstieg vom ersten bis zum fünften Jahr nach der Menarche zeigten, derart, dass in der 5-Jahres-Gruppe die FSH- und LH-Antworten eindeutig höher ausfielen als dies bei erwachsenen Frauen nach einer Dosis von 100 µg LHRH beobachtet wird. Diese gesteigerte hypophysäre Ansprechbarkeit auf LHRH ist auf die immer noch stetig zunehmende Sekretion von Oestradiol und Progesteron zurückzuführen, wobei die Progesteronwerte immer noch unter denen der Erwachsenen bleiben. Die basalen Prolactin-Werte waren signifikant höher als die bei erwachsenen Frauen beobachteten, mit einer leicht gesteigerten Prolactin-Antwort auf TRH-Stimulation und einer überschiessenden TSH-Antwort auf TRH, bei normlen T_3- und T_4-Werten.

Diese Ergebnisse zeigen, dass vom Einsetzen der Menarche bis zur komplexen und subtilen Regulation des Menstrualzyklus der Erwachsenen ein kontinuierlicher Reifungsprozess der hypothalamisch-hypophysär-gonadalen Achse abläuft, welcher ungefähr 5 Jahre dauert. Er ist gekennzeichnet durch zunehmende Ausschüttung von E_2, tiefe Progesteronsekretion und leicht erhöhte Prolactin-Werte, häufig zusammen mit einer Beeinträchtigung der lutealen Phase. Die gesteigerte Ansprechbarkeit der Hypophyse auf Releasing Hormone beruht auf einem positiven Feedback-Mechanismus des Oestradiols, welcher noch nicht mit einer für einen negativen Feedback ausreichenden Progesteronsekretion gekoppelt ist wie bei der erwachsenen Frau.

Demzufolge ist die Adoleszenz immer noch eine Reifungsperiode, und das Einsetzen der Ovulation ist der letzte Schritt in dieser Entwicklung.

Introduction

Puberty is characterized by progressive maturation of the hypothalamus-pituitary gonadal axis which, in girls, results in menarche.

During puberty, the basal secretion of steroids, gonadotrophins and prolactin increases regularly (3, 6, 10, 12, 16, 19, 36). Since the discovery of LHRH and TRH and their synthesis, the modulation of pituitary responsiveness by hormonal environment can be better characterized. Indeed, the gonadotrophin responses to exogenous LHRH have been found to rise throughout puberty, reflecting a progressive pituitary sensitivity (5, 13, 25, 32).

Upon the onset of menarche, neither plasma levels of sex steroids and gonadotrophins (6, 10, 19) nor the gonadotrophin responses to LHRH have reached adult levels (5, 13). Adolescence will thus be considered as a further important step in sexual development leading to the adult menstrual cycle characterized by the subtle positive and negative regulation of the hypothalamus-pituitary axis by sex steroids. Prolactin secretion also appears to play an important role in this maturation process (31).

An investigation was carried out in normal adolescent girls 1 to 5 years after menarche, the mean age of menarche being 13 years in Switzerland (34). The girls, 14 to 18 years old, attended guidance consultations to start with contraception.

Materials and methods

The 99 adolescents who participated in this study were divided into 3 groups, the first group consisting of 21 girls in the course of the first or second year after menarche; the second group of 52 adolescents in their third or fourth year after menarche, and the last group of 26 girls in their fifth year.

All the girls were tested for plasma levels of gonadotrophins, prolactin and TSH as well as for responses to LHRH and TRH. TSH, LH and FSH were determined by radioimmunoassay developed in the laboratory (20, 21), and prolactin by using a commercial kit (Hypolab S.A., Switzerland).

The stimulatory tests were performed by simultaneous i.v. injections of 50 µg of LHRH (Hoechst, Germany) and 200 µg of TRH (Roche, Switzerland) in the early follicular phase (6-8 days after the last menses) and in the luteal phase (21st-25th day of the cycle). In the luteal phase, in addition to pituitary hormones, estradiol, progesterone (24) and thyroid hormones (T_4, T_3) (4) were also determined in order to assess both the presence of ovulation and the euthyroid state.

Follicular and luteal phases are characterized in adult women by distinct secretions of both sex steroids and gonadotrophins (1, 9) as well as by various gonadotrophin responses to LHRH (22, 27, 44), but with no clear-cut differences in the responses of prolactin and thyrotrophin to TRH (33). No longitudinal study was performed throughout the menstrual cycle.

Table 1.

	No. of subj.		LRH test (50 µg i.v.) basal FSH	LRH test (50 µg i.v.) Δ FSH max.	LRH test (50 µg i.v.) basal LH	LRH test (50 µg i.v.) Δ LH max.	TRH test (100 µg i.v.) basal PRL	TRH test (100 µg i.v.) Δ PRL max.	TRH test (100 µg i.v.) basal TSH	TRH test (100 µg i.v.) Δ TSH max
			mU/ml		mU/ml		ng/ml		µU/ml	
Adolescents										
1st and 2nd year of menarche										
follicular phase	(13)	$\bar{X}$	4.7	1.9	*4.8	12.2	*10.3	34.2	3.7	25.6
		SEM	0.2	0.3	0.6	1.9	0.8	4.9	0.4	2.2
luteal phase	(8)	$\bar{X}$	3.3	3.1	*5.0	29.3				
		SEM	0.5	0.5	0.8	3.7				
3rd and 4th year of menarche										
follicular phase	(25)	$\bar{X}$	5.5	4.0	5.6	18.7	*11.9	32.1	*4.3	*35.9
		SEM	0.3	0.5	0.5	2.4	0.8	2.2	0.3	2.4
luteal phase	(27)	$\bar{X}$	3.2	4.7	8.5	37.6				
		SEM	0.2	0.9	1.2	3.2				
5th year of menarche										
follicular phase	(10)	$\bar{X}$	4.5	2.7	5.9	16.1	*9.3	29.6	3.5	*32.6
		SEM	0.3	0.7	0.6	2.4	0.6	2.5	0.4	4.2
luteal phase	(16)	$\bar{X}$	4.2	5.3	10.3	44.9				
		SEM	0.4	0.8	1.5	5.8				
normal adults				100 µg						
follicular phase	(21)	$\bar{X}$	4.9	2.8	7.4	14.9	7.1	25.8	3.0	22.0
		SEM	0.4	0.4	0.9	1.9	0.5	2.9	0.2	1.7
luteal phase	(21)	$\bar{X}$	3.4	2.4	7.2	33.3				
		SEM	0.2	0.3	0.8	3.0				

* statistically significant, compared with normal adults.

Results

The results obtained were compared to a group of 21 normal adult women (mean age: 27 years) who had also undergone two dynamic tests with 100 μg of LHRH and 200 μg of TRH respectively during the follicular and the luteal phases of the same menstrual cycle.
All results are summarized in Table 1 which shows the basal levels as well as the maximal increase of hormones after injection of releasing hormones.

1. Gonadotrophins

a) Basal levels: Plasma FSH reached adult concentration 1-2 years after menarche and did not change thereafter; in the first two years plasma LH values were significantly lower than those found in the adult women and increased later on to reach adult levels.

b) Gonadotrophin responses to LHRH: Comparison of LH and FSH responses to LHRH in adolescents to those in the adult females was not statistically possible on account of the lower quantity of LHRH used in the group of adolescents: 50 μg vs. 100 μg doses in the group of adults. Nevertheless, in the adolescents 1-2 years after menarche, the LH responses to LHRH, in both menstrual phases, were slightly lower than those found in the adult group represented in Fig. 1 by the shaded area, and the FSH responses were similar (upper panel). Three-four years after menarche, LH and FSH responses to LHRH were within the upper limit of the adults' range (Fig. 1, middle panel). The regular and progressive increase in LH and FSH responses to LHRH was still more evident in the 5-year group, resulting, in the luteal phase and in spite of the half dose received, in definitely higher LH and FSH responses than those observed in the adult women (Fig. 1, lower panel).

This enhanced pituitary responsiveness to LHRH is probably due to a still progressively increasing estradiol secretion. As shown in Table 2, mean plasma E_2 levels rose from 74 ± 15 pg/ml (mean ± SEM) within the 1-2 year post-menarche group to 114 ± 15 pg/ml within the 5-year post-menarche. In addition, E_2 and gonadotrophins have been shown to have significant daily variations at the end of puberty (29, 30). Mean plasma progesterone levels were

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Fig. 1. Gonadotrophin responses to 50 μg of LHRH in adolescents 1 to 5 years after menarche, tested during follicular and luteal phases (mean ± SEM).
The shaded area represents the mean ± SEM of gonadotrophin responses to 100 μg of LHRH obtained in a control group of 21 normal cycling women (mean age: 27 yr.). The adolescents were divided into 3 groups according to the years after menarche: 1-2 years, 3-4 years and 5 years. A progressive increase in LH and FSH responses to LHRH during the luteal phase is observed from 1 to 5 years post-menarche.
IU/ml of LH are referred to the 1st MRC International Reference preparation of human pituitary LH and FSH, code Nos. 68/40 and 68/39 respectively.

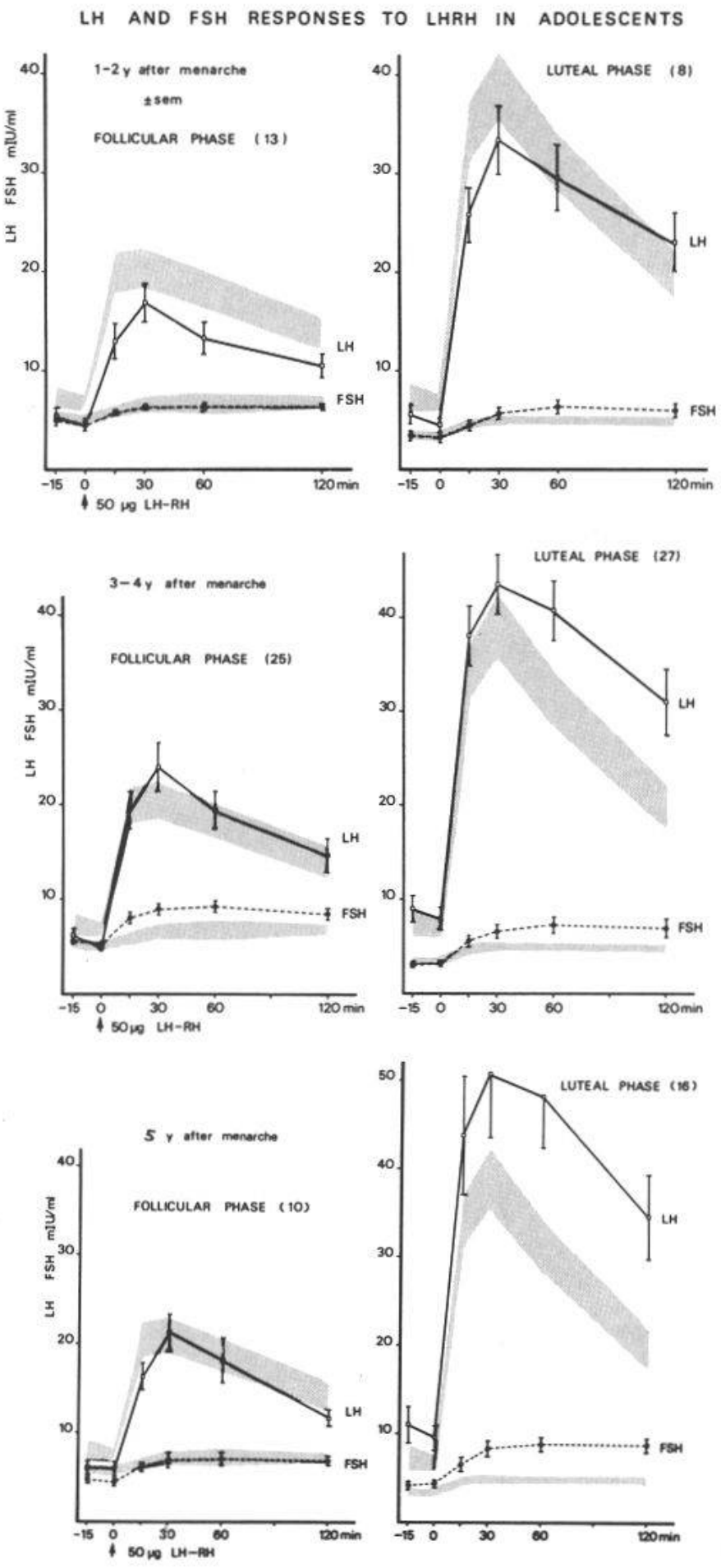
LH AND FSH RESPONSES TO LHRH IN ADOLESCENTS
1-2 y after menarche
±sem
FOLLICULAR PHASE (13)
LUTEAL PHASE (8)
3-4 y after menarche
FOLLICULAR PHASE (25)
LUTEAL PHASE (27)
5 y after menarche
FOLLICULAR PHASE (10)
LUTEAL PHASE (16)
LH FSH mIU/ml
LH
FSH
50 µg LH-RH
-15 0 30 60 120 min

Fig. 1

Table 2. Estradiol and progesterone plasma levels in adolescents during the luteal phase

Years after menarche		E_2 pg/ml	P ng/ml	Frequency of ovulatory cycles %
1 - 2 y	(9)	*74 ± 15	*2.82 ± 1.25	42
3 - 4 y	(25)	104 ± 16	*4.73 ± 1.01	56
5 y	(24)	114 ± 15	*5.45 ± 0.95	62
normal adults	(21)	136 ± 14	11.07 ± 1.46	100

() number of subjects Mean ± SEM
* statistically significant, compared with normal adults.

low in the 1-2 year post-menarche group and slowly increased from 1 to 5 years (Table 2), but remained still lower than those observed in normal adult females, confirming the high frequency of anovulatory cycles observed in these girls as well as frequently but slightly impaired corpus luteum function in spite of a sufficient gonadotrophin secretion.

2. Prolactin

a) Basal values: The important regulatory effects of estrogen on prolactin secretion were shown to appear at puberty, the basal prolactin levels being higher in girls than in boys (3). This study reveals that, throughout adolescence, prolactin secretion rose further since the mean basal prolactin levels were significantly higher than those found in the adult cycling women (Table 1).

b) Prolactin response to TRH: The prolactin response to TRH was slightly enhanced, compared with the adult group (shaded area), but decreased progressively from the 1st to the 5th year after menarche (Fig. 2, left panel).

3. Thyroid function

The thyroid does not present any significant modification during childhood and puberty (7). The adolescent girls studied displayed plasma T_4 and T_3 as well as TSH levels similar to those of a control group of 47 adult cycling women. T_3 increment, 120 min after administration of 200 µg of TRH, was also comparable to that observed in the adults (Table 3). The TSH response to TRH 1-2 years after menarche was not different from that found in the adult group, but it was increased in the 3-4 year group. Thereafter, the TSH response seemed to return progressively to adults' patterns (Fig. 2, right panel).

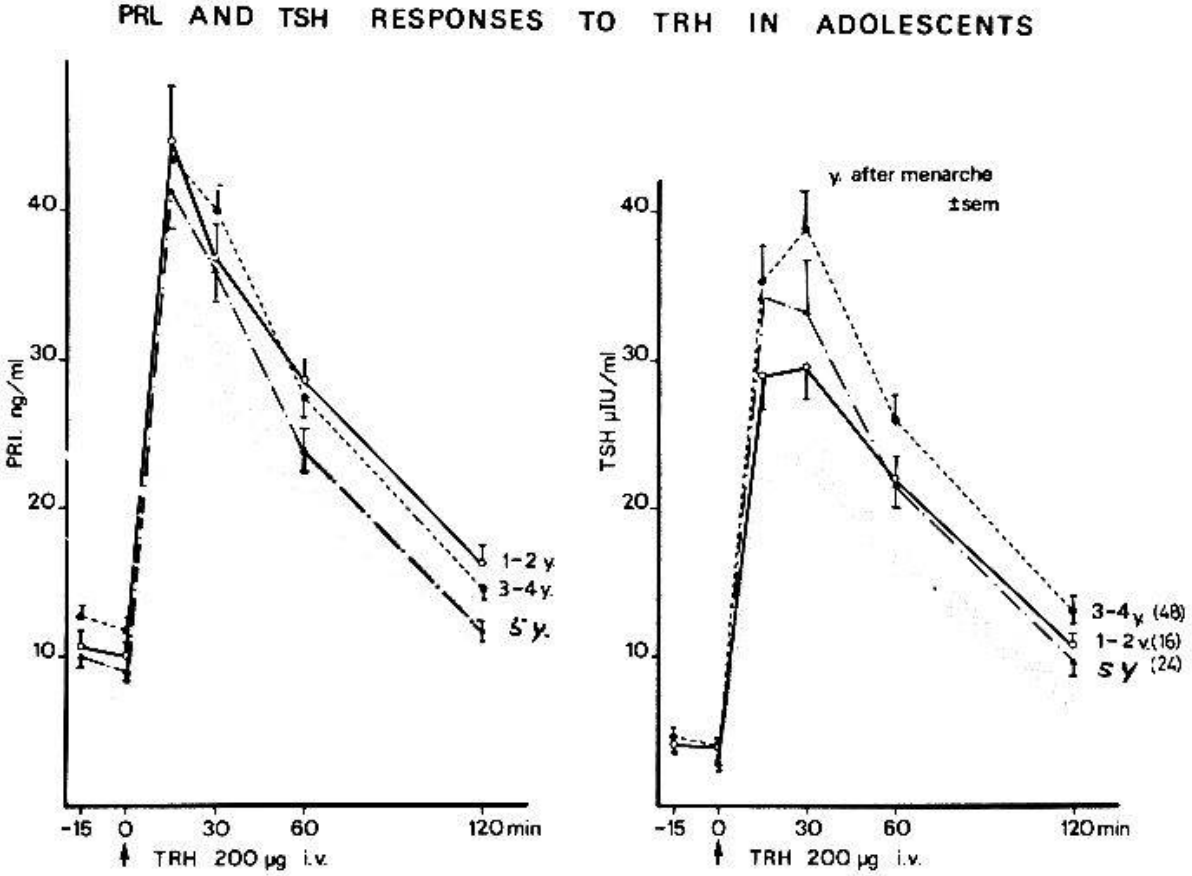

Fig. 2. Prolactin and TSH responses to 200 µg of TRH in adolescent girls. Left panel: Prolactin response to TRH in adolescents 1-5 years post-menarche is slightly, but not significantly, higher than that of the control group of 29 cycling women represented by the shaded area. Right panel: TSH response to 200 µg of TRH in the same groups of adolescents is slightly increased 3-4 years post-menarche in spite of normal T_4 and T_3 levels.

Table 3. Thyroid hormones in adolescent girls

Years after menarche		T_4 ng/ml Basal values	T_3 ng/ml Basal values	T_3 ng/ml 120 min after TRH
1 - 2 y	(21)	63.2 ± 2.3	1.53 ± 0.07	1.94 ± 0.10
3 - 4 y	(53)	67.3 ± 3.0	1.48 ± 0.08	1.97 ± 0.11
5 y	(24)	68.1 ± 5.0	1.55 ± 0.09	1.96 ± 0.12
normal adults	(47)	74.0 ± 2.0	1.49 ± 0.05	1.98 ± 0.07

() number of subjects Mean ± SEM

Discussion

These data show that, after menarche, the subtle and complex hormonal pattern, characteristic of the adult menstrual cycle, is not yet completely established. Thus, during the adolescent period, maturation of the hypothalamus-pituitary axis is still progressing, confirming previous reports (14, 40, 42). Indeed, adolescent girls disclose a regularly enhanced pituitary responsiveness to both LHRH and TRH as well as increasing basal LH and prolactin secretions.

The process of maturation in these adolescent girls could be attributed to gradual development of the positive feedback of estradiol at the hypothalamus and pituitary levels (11, 43). This stimulatory effect of estradiol on pituitary secretion might be due to both the progressive secretion of estrogens and the modulation of releasing hormones and steroid receptors. Indeed, experimental data have shown that estrogens increase the number of TRH binding sites in the rat pituitary (18); a similar action on LHRH binding sites could be postulated. Moreover, a self-priming effect of LHRH, also described in women (39), may play an important role during puberty and adolescence. However, this effect was observed only in the presence of adequate E_2 secretion and resulted in enhanced pituitary sensitivity to releasing hormone. It has also been observed in female rats (2). Moreover, dopamine could be involved in this enhanced pituitary responsiveness by a modification of its turnover rate by steroids in the hypothalamic area (8). Finally, SUTHERLAND et al. (38) have suggested that estrogen receptors could be modulated by the estrogen concentrations themselves.

All these regulatory effects seem to be more pronounced during the period of sexual development.

In pubertal rats, OJEDA and MCCANN (28) have reported a particularly high sensitivity of the pituitary to E_2, which they attribute to possible development or maturation of E_2 receptors at that period of life. Moreover, young animals are known to be more sensitive to any stimulatory or inhibitory effect of sex steroids than adult ones (23, 37).

In girls, the positive effect of E_2, which sets in during puberty, is thereafter modulated by progesterone. During the first years after menarche, the low but progressively increasing secretion of progesterone initially exerts a synergetic positive action together with E_2, resulting in a further increase in pituitary responsiveness to the same pulse of LHRH, as reported by LASLEY et al. (17). The well-known antiestrogenic action of progesterone seems to be effective only when adult levels have been reached. Indeed, in spite of its progessively increasing secretion, observed from 1 to 5 years after menarche, progesterone does not reach adult levels. An adequate concentration of progesterone (probably > 5 ng/ml) seems to be required to exert an antagonistic role on E_2, leading to a negative feedback on gonadotrophins, similar to what has been reported in the ewe (15). It is not so much the absence of this negative feedback by progesterone as its additive positive effect which is responsible for the enhanced responsiveness of gonadotrophins to LHRH in adolescent girls. Furthermore, this still inadequate progesterone secretion may reflect the slightly impaired corpus luteum function frequently observed in these girls, as well as the high frequency of anovulatory cycles, as shown in Table 2. Ovulation occurs at a rate of 42 % in the 1-2 year post-menarche, and increases

to 62 % in the 5-year group (41). In addition, the slightly enhanced prolactin secretion found in those girls could be one of the factors involved in irregular cycles and low progesterone secretion. Likewise, increased prolactin levels in the follicular fluid have been shown to impair the progesterone production in vitro (26); a similar inhibitory effect of prolactin on progesterone secretion has also been demonstrated in vivo (35).

In conclusion, from the onset of menarche to the complex and subtle adult menstrual cycle regulation, there is a progressive maturation of the hypothalamus-pituitary axis of the gonads which lasts approximately 5 years, as already suggested by WILDHOLM et al. (40). It is characterized by increasing E_2 secretion, low progesterone secretion and slightly increasing prolactin levels, leading to an enhanced responsiveness to releasing hormone, with frequently impaired luteal phases. Moreover, enhanced pituitary sensitivity to releasing hormones is due to the positive feedback mechanism of E_2 which is not yet associated with adequate progesterone secretion for a negative feedback, as in adult women.

The slow process of maturation is probably responsible for the frequent anovulatory and irregular cycles observed in adolescents.

Thus, adolescence is still a maturation period, the onset of ovulation being the last important step in this development, which makes it possible to distinguish between menstrual cycles before and after full maturation of the feedback mechanisms, as observed in adults.

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