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SEXUAL MATURATION IN GIRLS AND THE DEVELOPMENT OF ESTROGEN-INDUCED GONADOTROPIC HORMONE RELEASE

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SUMMARY

During all developmental stages of female puberty (P_1 - P_4) plasma LH and FSH concentration determined by radioimmunoassay decreased after a single i.m. injection of 50 μ g/kg estradiol-dipropionate in oil. This decrease coincided with the peaking level of circulating estradiol (measured by radioimmunoassay).

Only in the group of girls in an advanced stage of puberty (premenarche P_4) this initial nadir was followed by a secondary increase in plasma LH concentration but not in that of FSH. This secondary increase occurred during the period of decreasing level of circulating estradiol. However, only in two of the five girls at this advanced stage of puberty (P_4) the maximum of plasma LH approached the value of the preovulatory plasma LH peak in adult women. These results suggest that the potential for a stimulatory (positive) estrogen feedback response appears after mid-puberty at the stage P_4 .

It has been demonstrated in rats that the mechanism of the stimulatory (positive) feedback action of estrogen on gonadotropin release becomes operative at a low level of sensitivity long before estrarche. The concentration of circulating endogenous estrogen up to that time seems insufficient to trigger the release (PRESL *et al.*, 1968, 1972; CALIGARIS *et al.*, 1972). In contrast, in female rhesus monkeys estrogen induced gonadotropin surges were not demonstrable until some months after menarche (DIERSCHKE *et al.*, 1974). In the present study, serial determinations of plasma LH and FSH levels have been made in healthy prepubertal and pubertal girls to discover the stage of female sexual development at which the stimulatory estrogen feedback mechanism attains a level of sensitivity at which an acute increase in circulating estrogen concentration induced by a single administration of steroid is able to cause the characteristic gonadotropin release.

MATERIALS AND METHODS

The subjects were healthy girls. Each girl's sexual maturation was graded by secondary sex characteristics only, in accordance with the following criteria (utilizing a classification of JENNER *et al.*, 1972) : stage P₁-prepubertal (four girls), stage P₂-breast budding (mamma-areolata) and no more than sparse sexual hair (three girls), stage P₃ — mamma-areolata and moderate sexual hair (three girls), stage P₄ — mamma papillata and sexual hair which approaches the adult condition in amount and configuration (five girls), stage P₅ — postmenarcheal.

Each girl received a single intramuscular injection of 50 µg/kg of estradiol-dipropionate (EDP) in oil (Agofollin, Spofa).

Venous blood was obtained immediately before the injection of EDP and 24, 36, 48, 72 and 96 hours after injection, always between 9:00 and 10:00. The plasma was stored at -20°C until analysis, with all samples from each subject being assayed in duplicate in the same run.

The quantities of LH, FSH and estradiol (E₂) in plasma samples were determined by radioimmunoassay methods using KT40-7002 (LH) and KT40-3001 (FSH) kits (Serono, Roma) and ESTRK (E₂) kit (Sorin, Saluggia).

RESULTS

The mean plasma E₂ rose steadily throughout sexual maturation (fig. 1). After EDP administration, the circulating level of E₂ increased abruptly, peaking at 24-36 hours following intramuscular injection (fig. 2).

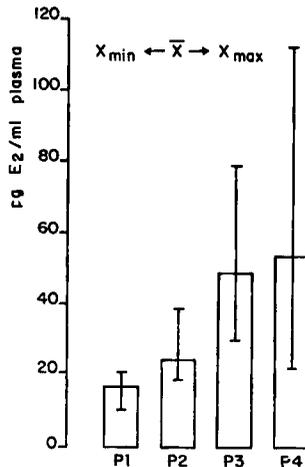


FIG. 1. — Plasma estradiol concentrations (pg/ml) throughout female puberty (means and ranges between minimum and maximum value) P₁-P₄ : stages of sexual maturation

The concentration of plasma LH generally decreased following EDP administration. Only in three of four prepubertal girls (P₁) the decline was not observed, but here the initial basal gonadotropin level was lower than 1.5 mIU/ml (fig. 3). The decrease was maximal during the period of the peak level of circulating E₂ and its intensity correlated significantly ($r = 0.86$) with the initial LH concentration in the

peripheral blood. Only in all premenarcheal girls (P_4) there appeared a marked secondary increase in plasma LH concentration coinciding with the decreasing level of circulating E_2 . This response can be shown more clearly by expressing the changes in plasma LH as a percentage of the initial concentration (an average increase of 483 p. 100) (fig. 4). Only in two of the five girls at this stage of advanced puberty a plasma LH concentration was attained which resembles the preovulatory LH peak in adult women (higher than 50 mIU/ml). At the stages from P_1 up to P_3 the plasma LH levels just as the levels of plasma FSH oscillated irregularly after the EDP injection, (fig. 5).

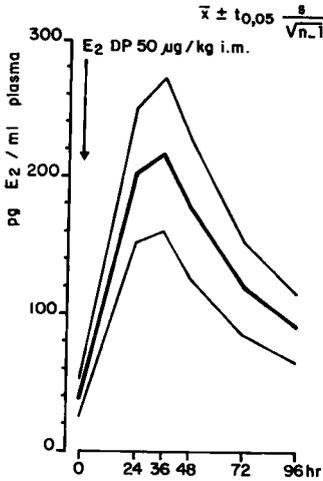


FIG. 2. — The mean plasma level of estradiol (pg/ml) after i.m. injection of 50 $\mu\text{g}/\text{kg}$ of estradiol-dipropionate in oil in 15 girls. The geometric means and the zone of 95 p. 100 confidence limits are plotted in the figure

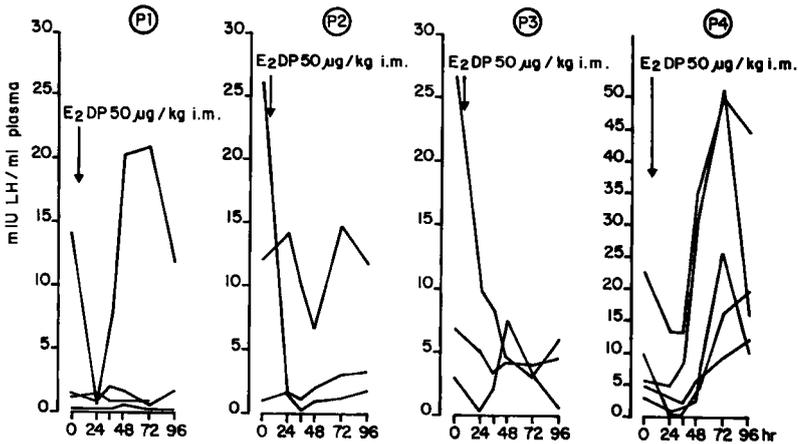


FIG. 3. — Changes in plasma LH levels (mIU/ml) after i.m. injection of 50 $\mu\text{g}/\text{kg}$ of estradiol-dipropionate in oil in separate stages of sexual maturation in girls (P_1 - P_4)

In premenarcheal girls (P_4), the pattern of response of plasma FSH concentration to EDP administration differed distinctly from that of LH. A secondary increase in circulating FSH level was observed only in one of the five girls, and the difference with the initial concentration was only + 40 p. 100 (fig. 6). At all stages of sexual maturation the characteristic response was merely a decrease of plasma FSH after EDP injection.

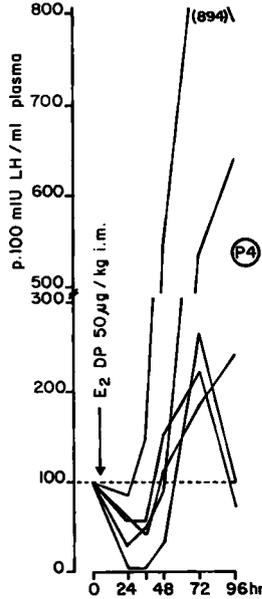


FIG. 4. — Changes in plasma LH levels (as percentages of the initial basal concentration) after estradiol-dipropionate administration in girls in advanced puberty (premenarcheal) (P_4)

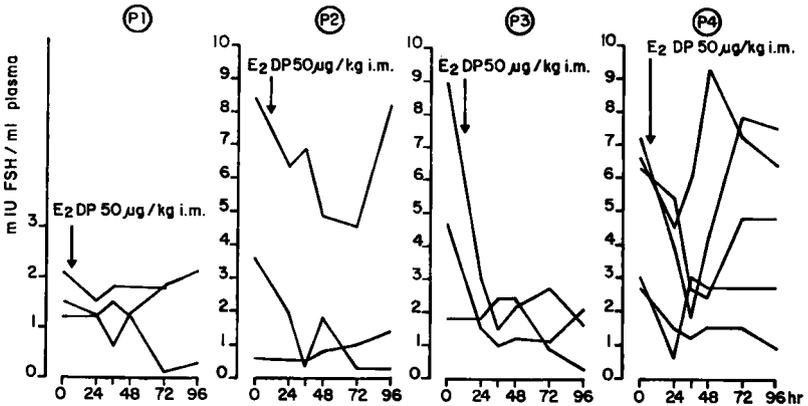


FIG. 5. — Changes in plasma FSH levels (mIU/ml) after i.m. injection of 50 µg/kg of estradiol-dipropionate in oil in separate stages of sexual maturation in girls (P_1 - P_4)

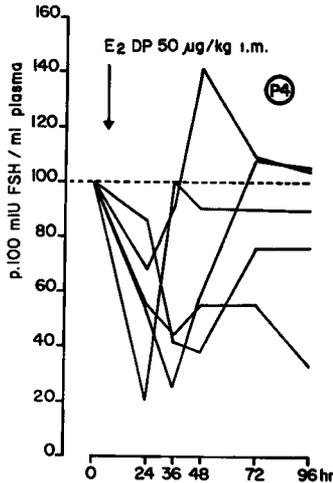


FIG. 6. — Changes in plasma FSH levels (as percentages of the initial basal concentration) after estradiol-dipropionate administration in girls in advanced puberty (premenarcheal) (P_4)

DISCUSSION

An increase in circulating E_2 level paralleling sexual maturation (fig. 1) agrees with the published data (JENNER *et al.*, 1972; BIDLINGMAIER *et al.*, 1973) and even our small group of girls demonstrates that the clinical classification is appropriate.

The observed primary decrease in plasma FSH and above all of plasma LH after EDP injection occurring during the period of peaking concentration of E_2 in the peripheral blood, appears to be comparable to the decrease demonstrated in adult women (NILLIUS and WIDE, 1971). Likewise the secondary increase in plasma LH in premenarcheal girls (P_4) coinciding with the decrease in circulating E_2 resembles the response in adult women, just as the absence of an increase in plasma FSH level (NILLIUS and WIDE, 1971).

The usual interpretation of the biphasic action of oestrogen upon the circulating LH concentration is that the increase in plasma E_2 level inhibits LH release, thereby supporting pituitary storage and, perhaps, stimulating gonadotropin synthesis too; the subsequent decrease in plasma E_2 level then probably acts as a trigger for LH release (YEN and TSAI, 1972; KORENMAN and SHERMAN, 1973; THOMPSON *et al.*, 1974). In this interpretation, the stimulatory estrogen feedback effect appears to be due to a rebound effect in a very sensitive biocybernetic system. Stored LH but not FSH is released; it seems that estrogen acts on pituitary FSH release in a different way. This concept does not assume the existence of a separate stimulatory feedback of estrogen on LH release. An alternative hypothesis, considers the increased LH release to be due to a separate stimulatory estrogen feedback. This view finds support in the following observation. In ovariectomized monkeys with circulating LH concentration depressed by means of subcutaneously implanted silastic capsules containing

crystalline E_2 , any further sudden increase in plasma E_2 level after estradiol-benzoate injection induces an initial mild LH decrease and then a characteristic impressive release of LH, evidently triggered by the preceding peak of E_2 (KARSCH *et al.*, 1973 a). The law of « all or nothing » does not apply here ; the circulating E_2 concentration must not only exceed a certain critical limit but the increase must persist during a certain period of time, which is shorter the higher the plasma E_2 level (KARSCH *et al.*, 1973 b). Stimulatory estrogen feedback is thought to be independent from and superposed to the inhibitory one, mediated by a different mechanism which develops separately (for review see PRESL, 1974). The presumption of this feedback as a manifestation of a mere rebound effect within a very sensitive inhibitory (negative) feedback mechanism appears to be highly improbable in the light of the present results, it emerges only in the late puberty group (P_4), but the sensitivity threshold of the inhibitory effect increases throughout sexual maturation in girls (KELCH *et al.*, 1973) and, therefore, is the highest in the late puberty group so that a resumed rebound effect should be only minimal.

Premenarcheal « maturity » of the stimulatory estrogen feedback in girls at the stage of advanced puberty (P_4) differs from that in subhuman primates : in premenarcheal monkeys, the attempts to induce an LH release by a single estradiol-benzoate injection failed, although LH-RH administration was effective. Only 4-8 months after menarche, exogenous estrogen is similarly effective (YAMAJI *et al.*, 1971 ; DIERSCHKE *et al.*, 1974).

In girls ad mid- to late puberty (P_3 - P_4), LH release was observed after clomiphene administration (KULIN *et al.*, 1972). A hypothesis was expressed, therefore, that the potential for a stimulatory estrogen feedback response appears after mid-puberty (KELCH *et al.*, 1973). Our present findings corroborate this concept (for review see GRUMBACH *et al.*, 1974).

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RÉSUMÉ

MATURATION SEXUELLE CHEZ LA FILLETTE ET MISE EN PLACE DE LA RÉTROACTION POSITIVE DES ESTROGÈNES SUR LES GONADOTROPINES

A toutes les étapes du développement pubertaire de la fille (P_1 - P_4) les concentrations plasmatiques de LH et FSH diminuent après une injection i.m. de 50 µg/kg de dipropionate d'estradiol en solution huileuse. La réduction des gonadotropines coïncide avec le maximum d'estradiol circulant (dosage radioimmunologique).

Dans le groupe de filles au stade le plus avancé (P_4 -préménarche) la diminution initiale des gonadotropines circulantes est suivie d'une augmentation de la concentration de la LH plasmatique mais pas de la FSH. Cette augmentation secondaire de la LH se produit quand le taux d'estradiol circulant diminue. Mais le taux maximum de LH observé n'approche les valeurs du pic préovulatoire de la Femme adulte que chez 2 sur 5 des filles au stade P_4 .

Ces résultats indiquent que la possibilité d'une rétroaction positive des estrogènes apparaît après la mi-puberté, au stade P_4 .

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