Premature thelarche: a possible adrenal disorder

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SUMMARY Endocrine studies in girls with precocious thelarche were compared with those of normal girls of similar ages. Girls with precocious thelarche showed breast development and oestrogenised vaginal smears as the only signs of precocious sexual development. A few of the girls were tall and some had advanced bone ages but these two findings were not consistently present in the same patient. Hormones—such as serum oestradiol, oestrone, $\Delta 4$ -androstenedione, progesterone, dehydroepiandrosterone (DHEA), follicle-stimulating hormone, luteinising hormone, and prolactin, and urinary 17-ketosteroids—were measured. Only DHEA was different, being higher in girls with precocious thelarche. It is suggested that the high DHEA level may serve as a precursor for conversion to oestrogens in the target tissues, breast, and vagina. This mechanism for oestrogenisation has been reported in other patients.

Premature thelarche is the term that Wilkins applied to describe precocious breast development in young girls who do not manifest any other sign of pubertal development.¹ Although premature thelarche is common in young girls, there have been few recent reports of the disorder.^{2–13} The aetiology is unclear. The results of endocrine evaluations in 24 girls are presented, and a possible adrenal aetiology is suggested.

Methods

Levels of prolactin, follicle-stimulating hormone (FSH), and luteinising hormone (LH) were assayed, using the kits of Biodata (Hypolab, Switzerland), by radioimmunoassay methods with double antibody. The Biodata hFSH standard was calibrated against the first international reference preparation IRP 69/104 MRC, and the hLH standard against the first IRP 68/40 MRC. Both reference preparations were obtained from the Medical Research Council, London. One milli-International Unit of the Biodata standard is equivalent to 1 mIU of the first IRP, or to 2 mIU of the second IRP. Coefficients of variation of plasma duplicate determinations were 6.5 and 7%.

Levels of oestradiol, oestrone, and progesterone were determined after extraction directly on dry residues. However because of the poor specificity of antisera, androstenedione and dehydroepiandrosterone were chromatographed on aluminium oxide microcolumn. The column was prepared according to Furuyama *et al.*¹⁴ Androstenedione was chro-

matographed as described by Judd and Yen.¹⁵ Radioimmunoassay of all steroids was performed with Biolab (Limal, Belgium) kits. Variation coefficients of plasma duplicate determination of oestradiol, oestrone, and progesterone were 9, 7, and 8%, and the sensitivity (2 SD of zero determinations) 4, 7, and 5 pg/tube respectively. Androstenedione and dehydroepiandrosterone were assayed with variation coefficients 13 and 14%, and sensitivity 8 and 14 pg/tube.

Urinary 17-ketosteroids were measured by a modification of the method devised by Callow *et al.*¹⁶

Breast development was estimated according to Tanner's stages of development.¹⁷

Vaginal cytology was interpreted by the method of Papanicolaou.¹⁸

Results

Patients. The 24 normal girls had each been admitted to the paediatric clinic at the University of Zagreb because of an infection from which each had recovered. Their ages ranged between 13 months and 7 years. There was no history of drug ingestion in either the mothers or the daughters. The blood samples were taken in the course of other routine investigations.

The 24 children with precocious thelarche had been referred because of breast development. Their ages ranged between 14 months and 7 years. The peak age of onset and presentation was between 1 and 3 years. Onset in 5 girls was at birth. Family history

Table Hormone concentrations in normal girls and girls with precocious thelarche

Parameter	Normal children				Precocious thelarche				<i>t</i> test	<i>P</i>
	<i>n</i>	Mean	SD	SE	<i>n</i>	Mean	SD	SE		
Δ4-androstenedione (ng/100 ml)	24	41.79	28.57	5.83	24	42.96	20.35	4.15	-0.160	0.874
Dehydroepiandrosterone (ng/100 ml)	24	144.08	98.53	20.11	19	203.47	75.37	17.29	-2.121	0.040
Progesterone (ng/ml)	22	0.623	0.516	0.110	19	0.485	0.268	0.062	1.023	0.312
Oestrone (pg/ml)	19	37.11	18.10	4.15	24	44.35	22.44	4.58	-1.117	0.271
Oestradiol (pg/ml)	19	20.11	15.18	3.48	24	23.70	17.30	3.53	-0.698	0.489
Follicle-stimulating hormone (mIU/ml)	22	4.21	2.93	0.62	24	4.28	2.28	0.43	-0.094	0.926
Prolactin (ng/ml)	22	22.14	12.43	2.65	22	25.23	12.01	2.56	-0.819	0.417

Conversion: traditional units to SI—Δ4-androstenedione: 1 ng/100 ml $\approx$ 0.0349 nmol/l; dehydroepiandrosterone: 1 ng/100 ml $\approx$ 0.0347 nmol/l; progesterone: 1 ng/ml $\approx$ 3.18 nmol/l; oestrone: 1 pg/ml $\approx$ 0.0037 nmol/l; oestradiol: 1 pg/ml $\approx$ 3.671 pmol/l.

showed precocious thelarche in three families: in the first it had been present in two siblings, in the second in the mother and daughter, and in the third family it had been present in the mother, a maternal aunt, and the daughter. Neurological examinations, skull x-ray films, special views of the sella turcica, and electroencephalograms were normal in every patient. The diagnosis of premature thelarche in these girls was based on isolated breast development in the absence of pubic hair. The gonadotrophin levels showed that these children were not in puberty. Furthermore, follow-up examination of the tallest girls showed no development of any other secondary sexual characteristic.

Clinical description. The height was above the 50th centile in 14 patients, 6 of whom were on the 90th centile or above. Only 2 of these 6 patients had significantly advanced bone age (>2 SD above the mean using the criteria of Greulich and Pyle). In 4 patients in whom the height was below the 90th centile, bone age was significantly advanced. In one child bone age was checked again at 26 months and was found to be no longer advanced. The tallest girl (for her age) was observed 5 and 10 months later and had not developed pubic hair. The right breast regressed at 10 months.

The course of breast development was variable. In none was there enlargement or elevation of the areolae. The breasts varied between Tanner's stages II and III. In 6 patients, breast development was unilateral and only one later developed bilateral breast enlargement. Three showed venous engorgement which later disappeared. In 4 children the consistency of the breast was noted to be softer on follow-up examination. None had pubic hair or acne. The labia majora and minora were prepubertal and no masses were shown by rectal examination. The uterus was palpable in none.

With the exception of 4 patients there was an increased number of intermediate cells on the vaginal smear ($>6\%$), reflecting mild to moderate oestrogenisation; in 3 patients, superficial cells were present, indicating pronounced oestrogen effect.

Hormones. Hormones in the normal girls are compared with those in the girls with precocious thelarche (Table). The mean level of dehydroepiandrosterone (DHEA) was higher in the girls with precocious thelarche. The mean level of the other hormones was similar in both groups regardless of age. In each girl the LH concentration was normal and appropriate for her age: in 19 of them the concentration was lower than 1.5 mIU/ml, and was thus below the sensitivity level. Therefore, LH values are omitted from further statistical evaluation. The urinary 17-ketosteroids were normal in each girl.

Discussion

The aetiology of premature thelarche has been variously attributed to increased sensitivity of breast tissue to low levels of oestrogens secreted during childhood^{19 20} or to increased ovarian oestrogen secretion.^{21 22}

To support the theory that it is due to increased ovarian oestrogen secretion, high levels of serum oestradiol have been found by some investigators^{4 8} and these have been attributed to increased gonadotrophins.⁵ Graafian follicles of the ovary have been noted in the newborn and young infant, and it was suggested that they were the source of the oestrogen.^{23 24} The follicles are thought to be the result of increased concentrations of gonadotrophin since birth.^{5 6} Others have proposed that there is an increase in the biologically active oestrogen because the unbound fraction is increased in the presence of normal total serum oestrogen. The increase in free oestradiol would result from a presumed decrease in sex hormone-binding globulin.⁹ Urinary-free oestradiol excretion has not been measured and this might be of interest in further studies.

In this series of patients with premature thelarche, no differences in prenatal or neonatal history were documented. There appeared to be an appreciable increase in height in several girls but this was not consistently associated with advanced bone age. In fact, several of the girls with advanced bone ages were not tall. Some investigators have reported

advanced stature and bone age in precocious thelarche but these have not been constant features of the disorder.^{5 6 21 25 26}

The breast development and vaginal smear indicate oestrogen effect. However, these changes cannot readily be attributed to increased oestrogen secretion as the serum oestradiol level was not particularly high. Indeed, any difference in hormones between the patients with premature thelarche and the control group is not obvious. There was no increase in any pituitary hormone, specifically no increase in FSH, LH, or prolactin. These findings agree with previous reports.^{6 7 10–12} Job *et al.*⁶ found an increased gonadotrophin reserve on luteinising hormone releasing factor testing but resting FSH and LH were in the prepubertal range. There was an increase in DHEA in the patients reported here. The hormonal level of DHEA in normal prepubertal children is in the upper range of normal as reported previously.²⁷ Since the methods were the same for both groups of children, the difference in the serum DHEA concentration between the two groups is statistically valid. DHEA is of adrenal origin in the prepubertal child. We suggest that the increased adrenal DHEA, observed in our patients, may serve as precursor for the peripheral conversion to oestrogens. Support for this suggestion is derived from the report of MacDonald *et al.*²⁸ who demonstrated peripheral conversion of DHEA to oestradiol in ovariectomised women.

The increased level of DHEA in the patients may be converted to oestradiol in the breasts. This may represent an appreciable source of oestrogen in the prepubertal child. This mechanism may apply to the vaginal mucosa also. Although MacDonald *et al.*²⁸ reported only a small percentage conversion of DHEA to oestradiol in the periphery, this may represent a significant oestradiol level at the target tissue if the DHEA level is raised. The capacity of DHEA-S to oestrogenise the vaginal mucosa was reported by Drucker *et al.*²⁹ who administered DHEA-S to a 3-month-old girl and demonstrated vaginal oestrogenisation which reverted to normal when treatment was stopped. These investigators proposed that DHEA-S was hydrolysed in the vaginal mucosa to oestrogen precursors as has been reported in the adult vagina.³⁰ A further role for DHEA as an oestrogen precursor for the brain has been suggested since immature rats treated with DHEA produced a surge of FSH, LH, and prolactin, in addition to precocious ovulation.³¹

The mechanism for the development of premature thelarche proposed here may indeed be the mechanism for the initiation of normal pubertal breast development.³² Since adrenal androgens begin to

rise before the advent of increased gonadotrophins,³³ the adrenal androgens may serve as local precursors for oestrogen in the breast and may initiate breast development in the absence of high serum levels of biologically-active oestrogens. Thus, the aetiology of premature thelarche may be precocious secretion of adrenal androgens converted to oestrogens by the immature breast. Local conversion may also explain the oestrogenisation of the vagina.²⁹

In precocious adrenarche too, there is increased secretion of adrenal androgens associated with precocious pubic hair development in the absence of breast development.³⁴ In such children, the vaginal smear has been noted to be oestrogenised.^{26 35 36} These findings suggest that variability of local tissue conversion of androgens to oestrogens may govern the clinical presentation of increased adrenal androgens.²⁸

The diagnosis of premature thelarche requires absence of other secondary sexual characteristics during a prolonged period of time. Thus it is possible that some of these patients were in the earliest stages of puberty. Nevertheless, it is interesting that with manifestations of breast development and oestrogenised vaginal smears, only the level of adrenal DHEA was found to be increased.

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Received 13 February 1981