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Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens

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Precocious puberty is generally defined as the appearance of secondary sex characteristics before age 8 years in girls (or menarche before age 9 years) and before 9 years in boys. The overall incidence of sexual precocity is estimated to be 1:5000 to 1:10 000 children. The female-to-male ratio is ~10:1. In addition to the psychosocial disturbances associated with precocious puberty, the premature pubertal growth spurt (with less time for prepubertal growth) and the accelerated bone maturation result in reduced adult height. Precocious puberty may be gonadotrophin-dependent [i.e. of central origin with premature activation of the gonadotrophin-releasing hormone (GnRH) pulse generator] or gonadotrophin-independent (i.e. peripheral where the GnRH pulse generator is suppressed). This can be determined by GnRH testing. The pathophysiology is the basis for different diagnostic and therapeutic strategies, i.e. in the first case a stimulated LH/FSH ratio >1 and suppressive treatment with GnRH agonists (e.g. in hypothalamic hamartoma), and in the second decreased gonadotrophins and removal or suppression of the endogenous or exogenous sex steroid source (e.g. congenital adrenal hyperplasia). While several cases of gonadotrophin-independent precocious puberty due to oestrogen exposure via the transdermal, oral, or inhalative route have been reported, no case is known with the development of subsequent secondary central precocious puberty. Food contamination with oestrogens is theoretically possible, but would most probably be sporadic and, thus, would not lead to precocious puberty. As steroid hormones in meat production are banned in the European Union, no data on the impact of environmental oestrogenic substances on human maturation are currently available. In conclusion, the risk for children to develop precocious puberty through exposure to oestrogens (or androgens) in the environment or in food is very low. Nevertheless, studies of the effects of defined environmental oestrogenic substances on the human reproductive system and on pubertal development are warranted.

Key words: central precocious puberty/GnRH test/hypothalamic hamartoma/oestrogen contamination/precocious pseudopuberty

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Introduction

Precocious puberty is a condition that has a profound impact on growth, development and psychosocial well-being of the patient. From studies of untreated patients the long-term outcome is known to include short stature, body disproportion and obesity (Thamdrup, 1961; Sigurjonsdottir and Hayles, 1968; Sorgo *et al*., 1987). In addition to the long-term physical sequelae of precocious puberty, there is the potential risk of sexual abuse due to the premature sexual development (Thamdrup, 1961; Herman-Giddens *et al*., 1988). Pregnancies in very young children have been described (Stoeckel, 1938; Ehrhardt *et al*., 1984). Thus, diagnosis and adequate treatment are of paramount importance to ensure normal physical and psychological development of these children. This paper provides an overview of the pathophysiology and aetiology of precocious puberty with special

emphasis on hypothalamic hamartoma as a typical example for central precocious puberty and on exogenous oestrogens as a cause of peripheral sexual precocity with possibly increasing frequency.

Definition

Puberty is the period during which human development progresses from the first pubertal sign to full sexual maturation. Within this period the capacity for reproduction is achieved. Puberty includes the development of secondary sexual characteristics as well as growth, development, and maturation of primary sexual organs. Pubertal development that occurs too early is defined as precocious. Thus, the definition of precocious puberty is based on the early age limits for the onset of puberty in the normal population. Ethnic differences have to be taken into account (Herman-Giddens *et al*., 1997).

In girls, precocious puberty is most commonly, however, arbitrarily defined by the appearance of breast development (thelarche) before the 8th birthday and/or menarche before the 9th birthday. These diagnostic threshold ages were derived from studies of normal pubertal development which showed that Tanner stage B2 is present at 10.9 ± 1.2 (± 1 SD) years of age in Swiss girls (Largo and Prader, 1983b) and at 11.2 ± 1.1 years in British girls (Marshall and Tanner, 1970). Menarche was seen at a mean age of 13.4 ± 1.1 years and 13.5 ± 1.02 years in the Swiss and British girls respectively. Thus, the diagnostic age for thelarche corresponds to approximately –2.5 SD below the normal mean age while the threshold age for menarche is in the range of –4 SD. From these figures it becomes clear that the ages accepted for diagnosing precocious puberty were chosen somewhat arbitrarily. Two percent of healthy girls may show a pubertal stage B2 before their 8th birthday (Largo and Prader, 1983b). A more recent cross-sectional study in paediatric practices in the USA (Herman-Giddens *et al*., 1997) suggested that the onset of puberty may be substantially earlier in girls (B2 9.96 ± 1.82 years in white American girls) than reported in former studies. Several methodological problems of this American paediatric practice study have been discussed by the authors themselves (Herman-Giddens *et al*., 1997) and the major inherent bias is that the patient sample was not randomly selected from the normal population.

A recent cross-sectional study of a large number of East German girls investigated between 1984 and 1986 (Engelhardt *et al*., 1995) showed that start of puberty (B2: 10.8 years = 50th centile, 8.49 years = 3rd centile) and menarche (13.46 years = 50th centile, 11.3 years = 3rd centile) occurred at a very similar age as reported in the earlier Swiss and British longitudinal studies (Marshall and Tanner, 1970; Largo and Prader, 1983). Thus, at least for East Germany there seems to be no trend to an earlier start of puberty in girls. A recent investigation of menarcheal age in North German schools has shown a mean age at menarche of 12.9 years (unpublished observation) which is completely in accordance with the American data (Herman-Giddens *et al*., 1997). The question why the length of time between thelarche (B2) and menarche was increased in the latter study (2.92 years) as compared to all other studies mentioned above (2.3-2.5 years) remains unanswered and may be the consequence of a differing patient selection bias at different ages. However, a continuing secular trend to an earlier age at menarche (median age at menarche 1955: 13.66 years; 1965: 13.40 years; 1980: 13.28 years; 1997: 13.15 years) was reported from The Netherlands (Fredriks *et al*., 2000).

In boys, precocious puberty is usually defined as gonadarche (Tanner stage G2 and/or one-sided testicular volume ⩾3 ml) or pubarche (Tanner stage P2) before the 9th birthday. For comparison, normal age for G2 reported in the literature was 10.8 years (Willers *et al*., 1996; 50th centile), 11.2 ± 1.5 years (Largo and Prader, 1983a), and 11.6 ± 1.07 years (Marshall and Tanner, 1969). Start of pubertal testicular growth in healthy boys defined as a one-sided testicular volume of at least 3 ml was seen between the ages of 11.8 ± 0.9 years (Largo and Prader, 1983a) and 12.2 years (Biro *et al*., 1994). Three and two per cent of normal boys may show a testicular volume of at least 3 ml and Tanner stage G2 before their 9th birthday, respectively (Largo and Prader, 1983a). In contrast to the trend in pubertal development in girls, a slight age increase for Tanner stage G2 in boys was seen between 1955 and 1997 in The Netherlands (Fredriks *et al*., 2000).

Epidemiology

Scientifically sound epidemiological data of precocious puberty are not available in the literature. It is estimated that precocious puberty occurs in 1:5000 to 1:10 000 children (Gonzalez, 1982). In patients with central nervous system (CNS) disorders or CNS lesions the incidence is much higher. For instance, in neurofibromatosis type I, 2.4-5% of patients develop precocious puberty (Habiby *et al*., 1995, 1997; Cnossen *et al*., 1997; Carmi *et al*., 1999; Virdis *et al*., 2000), in neonatal encephalopathy the frequency is 4.3% of girls (Robertson *et al*., 1990). In patients with hydrocephalus the incidence is as high as 10-11% (De Luca *et al*., 1985; Kaiser *et al*., 1989; Lopponen *et al*., 1996). Patients with meningomyelocoele have a predisposition for precocious puberty that occurs in 5-18% of affected children (Meyer and Landau, 1984; Trollmann *et al*., 1996). Recently, some congenital dysmorphic syndromes were shown to be associated with an increased frequency of precocious pubertal development (Scothorn and Butler, 1997; Cherniske *et al*., 1999; Partsch *et al*., 1999b).

Pathophysiology

Normal pubertal development is caused by the increasing pulsatile activity of the hypothalamic gonadotrophin-releasing hormone (GnRH) pulse generator which leads to the maturation of pituitary gonadotrophin release (pulsatile LH and FSH secretion) and subsequently to the maturation of gonads and gonadal activity. For the initiation of puberty a functioning GnRH neuronal network and pulsatile GnRH secretion are critical prerequisites. The central mechanisms governing GnRH secretion are located within the neuronal and the glial networks (Ojeda, 1994; Ojeda *et al*., 1995; Terasawa, 1995). To date, it is believed that two mechanisms are responsible for the central control of pulsatile GnRH secretion: (i) a tonic inhibitory restraint, and (ii) excitatory inputs to GnRH neurons (Bourguignon *et al*., 1995). While γ-aminobutyric acid (GABA) and $GABA_A$ receptors are important components of the tonic inhibitory system, excitatory

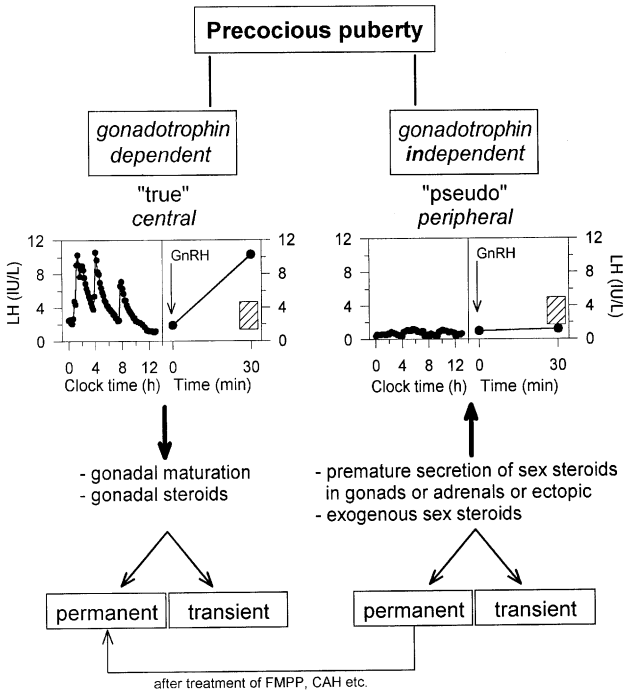

Figure 1. Pathophysiology scheme of precocious puberty. CAH = congenital adrenal hyperplasia; FMPP = familial male precocious puberty.

amino acids such as glutamate and its receptor and probably also transforming growth factor (TGF)-α play the major role in the excitatory system (Bourguignon *et al*., 1995; Ojeda *et al*., 1995). In the case of precocious puberty, this type is called central precocious puberty as it originates from the central part of the feedback loop governing human reproduction. Hormone concentrations and responses to stimulation tests are consistent with gonadarche, however, with increased gonadotrophin concentrations relative to the pubertal stage in many patients (Partsch *et al*., 1989; Oostdijk *et al*., 1995). Spontaneous LH secretion is pulsatile, particularly at night. In analogy to normal puberty, this type is also termed 'true' or gonadotrophin-dependent precocious puberty (Figure 1, left side).

In contrast to the central type of precocious puberty, pubertal development may also be caused by the premature secretion of sex steroids originating either from the gonads or from other sources or resulting from exogenous exposure. Thus, the origin of the hormonal trigger of puberty is not located centrally at the GnRH pulse generator but peripherally. It corresponds with the logic of a negative feedback system that central hormonal activity is suppressed. Therefore, gonadotrophin pulsatility is absent and responses to GnRH stimulation are low (Figure 1, right side). Since puberty is not the result of the activity of the normal cascade of hormonal events it is termed precocious 'pseudopuberty' or gonadotrophin-independent or peripheral precocious puberty.

It is important to differentiate between central precocious puberty and the peripheral types of precocious puberty because of the differences in differential diagnoses (Tables I and II) and because of the fundamentally different treatment options. While medical treatment of central precocious puberty by long-acting GnRH agonistic analogues is irrespective of the aetiology (Comite *et al*., 1981; Crowley *et al*., 1981; Laron *et al*., 1981; Roger *et al*., 1986; Oostdijk *et al*., 1990; Partsch *et al*., 1999c), the treatment of gonadotrophin-independent precocious puberty is more diverse and highly dependent on the underlying disease.

Gonadotrophin-dependent precocious puberty

For central precocious puberty, estimates of the female-to-male sex ratio range from 3:1 (Kappy and Ganong, 1994) to 23:1 (Bridges *et al*., 1994). Central precocious puberty may be permanent or transient (Table I). The recognition of transient forms is of particular importance in order not to initiate unnecessary treatment in these patients (Partsch *et al*., 1998; Palmert *et al*., 1999) and not to attribute outcome results to an unjustified treatment (Partsch *et al*., 1999c). It is interesting to note that in some rare cases organic central precocious puberty may also be transient (Brauner *et al*., 1987). Central precocious puberty does not present as a homogeneous clinical picture, but is much more a continuum of clinical presentation and rate of progression ranging from slowly progressive or transient forms to rapidly progressive forms (Pescovitz *et al*., 1986; Kreiter *et al*., 1993; Partsch *et al*., 1998; Palmert *et al*., 1999; Léger *et al*., 2000).

Until now, even with the use of modern imaging techniques, the majority of central precocious puberty patients do not show any CNS lesion or any underlying pathology. This condition is thus termed idiopathic central precocious puberty. The estimation of the percentage of idiopathic cases within central precocious puberty varies from 69 to 98% in girls and from 0 to 75% in boys (Table III). This means that in boys with central precocious puberty the search for an underlying pathology (tumour) needs to be much more rigorous. Furthermore, the likelihood of detecting an organic cause of precocious puberty is higher the younger the child. An overview of the various aetiologies is given in Table I. These include a variety of brain tumours and brain malformations.

Hypothalamic hamartoma

Due to improved imaging methodology the number of patients diagnosed as having a hypothalamic hamartoma is probably increasing. Hypothalamic hamartomas are congenital, non-neoplastic tumour-like lesions formed by heterotopic grey matter, neurons, glial cells and fibre bundles in variable proportions (Inoue *et al*., 1995). They are usually located at the base of the brain at the floor of the third ventricle, near the tuber cinereum or near the mamillary bodies. Since they are congenital malformations, hypothalamic hamartomas frequently cause precocious puberty at an early age (Partsch *et al*., 1999a), sometimes starting at birth (Albright and Lee, 1992; Guibaud *et al*., 1995; de Brito *et al*., 1999), but may also be asymptomatic (Sato *et al*., 1985; Arita *et al*., 1999) or may be found by chance at autopsy (Sherwin *et al*., 1962). Some hypothalamic hamartomas are associated with gelastic seizures which may be resistant to anticonvulsive treatment (Marliani *et al*., 1991; Cascino *et al*., 1993; Nishio *et al*., 1994; Fukuda *et al*., 1999).

The incidence of hypothalamic hamartomas in the normal population is not known. Recent studies, employing modern techniques of imaging in large series of patients with central precocious puberty, have shown that hypothalamic hamartomas are responsible for sexual precocity in 10-28% of these children (Lyon *et al*., 1985: 28%; Hibi and Fujiwara, 1987:

Table I. Aetiology of central precocious puberty (gonadotrophin-dependent, 'true')

Category	Underlying disease
Permanent precocious puberty	
Idiopathic	Sporadic
	Familial
CNS abnormalities or lesions	Hypothalamic hamartoma
	Tumours: astrocytoma, craniopharyngioma, ependymoma, glioma, LH-secreting adenoma, pinealoma
	Congenital malformations: arachnoid cyst, suprasellar cyst, phakomatosis, hydrocephalus (± spina bifida), septo-optic dysplasia
	Acquired disease: inflammatory CNS disease, abscess, radiation, chemotherapy, trauma
Dysmorphic syndromes	Williams-Beuren syndrome
	Klinefelter syndrome (rare)
CNS maturation with central precocious puberty secondary to prolonged sex steroid exposure:	Congenital adrenal hyperplasia
	Sex steroid-producing tumours
	Male-limited precocious puberty (constitutively activated LH receptor)
Transient precocious puberty	Idiopathic sporadic
	Arachnoid cyst
	Hydrocephalus
Variants of pubertal development (partial or incomplete precocity)	Premature thelarche
	Premature pubarche
	Premature menarche

14%; Sharafuddin *et al*., 1994: 11.5%; Kornreich *et al*., 1995: 12.9%; Robben *et al*., 1995: 10%; Partsch *et al*., 1999c: 21%).

Hypothalamic hamartomas contain GnRH-secreting neurons and it is believed that they function as an accessory GnRH pulse generator outside the physiological feedback loop (Judge *et al*., 1977; Hochman *et al*., 1981; Price *et al*., 1984; Culler *et al*., 1985; Inoue *et al*., 1995). However, it has recently been shown that TGFα is an important facilitatory component of the central control of puberty (Ojeda *et al*., 1995) and that TGFα receptors are expressed in astroglial cells present in hypothalamic hamartomas (Jung *et al*., 1999). Together with other findings concerning the role and function of glial cells (Ojeda, 1994) these observations open the possibility that precocious puberty in hamartoma patients may be caused by changes in glial cell activity and by the influence of glial cell products on hypothalamic GnRH neurons (Jung *et al*., 1999). In addition, there are differences in the pituitary response to exogenous GnRH between patients with hypothalamic hamartoma and those with idiopathic precocious puberty suggesting different changes in the neuroendocrine regulation (Uriarte *et al*., 1998). Magnetic resonance imaging (MRI) is of particular importance in the diagnosis of hypothalamic hamartomas since histological examination will not be carried out in most patients. The typical MRI picture is that of an isointense structure on T1-weighted images which may be isointense or slightly hyperintense on T2-weighted images.

The question of the adequate and optimal treatment of children with hypothalamic hamartoma and precocious puberty has been discussed controversially in the literature (Siegel-Witchel, 1995). In general, however, the paediatric, and recently, also, the neurosurgical recommendation is that long-acting GnRH agonists are the first choice of treatment in patients with hypothalamic hamartomas and precocious puberty (Stewart *et al*., 1998; Feuillan *et al*., 1999; Partsch *et al*., 1999a). Successful suppression treatment has been reported by several groups for a duration of up to 8.4 years (Comite *et al*., 1984; Mahachoklertwattana *et al*., 1993; Chamouilli *et al*., 1995; Stewart *et al*., 1998; de Brito *et al*., 1999; Feuillan *et al*., 1999; Ishii *et al*., 1999). Long-term studies and outcome data after treatment with GnRH agonists are favourable and do not show negative sequelae (de Brito *et al*., 1999; Feuillan *et al*., 1999; Heger *et al*., 1999). In particular, depot preparations ensure an adult height within the genetic height potential with normal body proportions, bone density and reproductive function (Heger *et al*., 1999).

Secondary central precocious puberty

Conditions that lead to long-term exposure to sex steroids and thus to accelerated growth, bone age acceleration and maturation of hypothalamic centres important for the initiation of puberty, may lead to secondary central precocious puberty when treated. Treatment of the primary disease causes a drop in sex steroid concentrations and thereby activates the hypothalamic GnRH pulse generator via the prematurely matured feedback system. This form of precocious puberty may complicate the course of congenital adrenal hyperplasia (Pescovitz *et al*., 1984; Pouw *et al*., 1986; Boepple *et al*., 1992; Dacou-Voutetakis and Karidis; 1993; Soliman *et al*., 1997; Frenzel and Doerr, 1998) or familial or sporadic male-limited precocious puberty (Holland *et al*., 1987; Laue *et al*., 1993; Gromoll *et al*., 1998; Leschek *et al*., 1999).

Table II. Aetiology of peripheral precocious puberty (gonadotrophin-independent, 'pseudopuberty')

Category	Underlying disease
Ovarian disorders	Granulosa cell tumour
	Theca cell tumour
	Other oestrogen-secreting tumours: teratoma, teratocarcinoma, dysgerminoma, luteoma, mixed cell tumour, lipoid tumour
	Sex-cord or Sertoli-cell tumour of the ovary with annular tubuli seminiferi (SCTAT) and aromatase activity in Peutz-Jeghers syndrome
	McCune-Albright syndrome (ovarian cysts)
	Autonomous isolated ovarian cysts
Testicular disorders	Leydig cell adenoma
	Constitutively activating LH receptor mutation (male-limited precocious puberty = testotoxicosis)
Adrenal disorders	Adrenal adenoma
	Adrenal carcinoma (usually virilizing)
	Congenital adrenal hyperplasia (21-hydroxylase or 11β-hydroxylase deficiency)
HCG-secreting tumours	Dysgerminoma, teratoma, chorioepithelioma, choriocarcinoma, hepatoblastoma, pinealoma
Exogenous	Sex steroid exposure: pills (oestrogens; anabolics), food additives, cosmetics, creams etc.
Transient precocious puberty	Autonomous isolated ovarian cysts (self-limiting)
	Exogenous (interruption of exposure)

HCG = human chorionic gonadotrophin.

Table III. Frequency (%) of idiopathic forms of central precocious puberty (excluding secondary central precocious puberty) in girls and boys. Precocious puberty was defined as start of pubertal development before age 8 years in girls and before age 9 years in boys.

Reference	Idiopathic central precocious puberty (%)		
	All	Girls	Boys
Thamdrup (1961) $n = 56$	67.9	75.6	36.4
Pescovitz *et al*. (1986) $n = 107$	57.9	69	10
Kaplan and Grumbach (1990) $n = 205$	65.4	72.9	33
Brauner and Rappaport (1993) $n = 294$	62.6	70.1	28.3
Bridges *et al*. (1994) $n = 95$	89.5	93.4	0
Kappy and Ganong (1994) $n = 640$	61.6	74	28
Carel *et al*. (1999)* $n = 66$	95.5	98	75
Heger *et al*. (1999) and Partsch *et al*. (1999b) $n = 90$	-	73.3	-
Cisternino *et al*. (2000) $n = 304$	-	74.4	-
De Sanctis *et al*. (2000) $n = 45$	-	-	60

*Definition of precocious puberty in boys: start of puberty <10 years of age.

Secondary central precocious puberty has also been described in single patients with the McCune-Albright syndrome (Kaufman *et al*., 1986; Schmidt and Kiess, 1998; Feuillan *et al*., 1993). In the literature there is one single case of transient central precocious

Table IV. Precocious pseudopuberty (gonadotrophin-independent) in children after ingestion or dermal exposure to oestrogen-containing food or ointments

Reference	*n*/sex	Age (years)/ breast stage (B)	Plasma oestradiol (pg/ml)	Mode of exposure	Substance and dose
Hesselvik (1952)	1/m	0.8/B3	-	Transdermal	DES
Prouty (1952)	1/m	4/B3	-	Transdermal + inhalation	DES (dust from tablet-making machine)
Cook *et al*. (1953)	2/f	4–7/B2–3	-	Ingestion	DES (2 mg/day for 4 weeks)
Green (1958)	2/1f + 1m	2–3/B3	-	Ingestion + transdermal	DES (pellets and paste on poultry farm)
Hertz (1958)	4/1f + 3m	5–10/B2	-	Ingestion	Oestrone/150 µg per day
Weber *et al*. (1963)	7/4f + 3m	1.7–8.6/ B2–3?	UE undetected	Ingestion	DES contamination of INH tablets (12–90 µg/day)
Landolt and Mürset (1968)	4/1f + 3m	0.25–9/B2-3	-	Transdermal + ingestion	DES in hair lotion or ointment (25–250 mg/child)
Beas *et al*. (1969)	7/3f + 4m	0.3–2/B2–4	-	Transdermal	Oestrogenic effect equivalent to 0.1 mg oestradiol benzoate
Fara *et al*. (1979)	323/110f + 223m	3–14/B2	Slightly increased	Ingestion?	Oestrogens in uncontrolled poultry and beef?
Ramos and Bower (1969)	1/f	3.3/B2	UE 4 µg/24 h	Transdermal	Oestrogens in facial cream (2500 units/6 months)
Kimball *et al*. (1981)	8/7f + 1m	B2–3	-	Ingestion?	Oestrinyl in cow's milk?
Edidin and Levitsky (1982)	1/m	5/B3	114	Hair cream	1.01 mg 'natural' oestrogens per 2 oz jar hair cream
Pasquino *et al*. (1982)	3/f	0.75–7/B2	<10	Ingestion?	Not clarified (oestrogen-contaminated meat suspected)
Halpérin and Sizonenko (1983)	1/m	6.5/B3	14	Transdermal	Oestrone, diethylstilboestrol, extracts of ovaries
Freni-Titulaer *et al*. (1986)	120/f	0.5–8/B2	-	Not known	No risk factors or substances found
Nizzoli *et al*. (1986)	73/45f + 28m	1–2/B2	-	Not known	No risk factor found besides residence in Milan
Peter *et al*. (1995)	1/f	2/B2–3	20	Transdermal	330 µg 17β-oestradiol/day
Zimmerman *et al*. (1995)	8/-	-/-	Normal	Transdermal	Oestrogens in hair care products
Tiwary (1998)	4/f	1–7.5/B1–3	6	Transdermal	Oestriol (16–20 mg/g), 17β-oestradiol (0.04 mg/g) in hair products
For comparison:					
Illig *et al*.	9/f	11.7–14.4/	6.8 ± 1.7	-	No therapy
(1990)	UTS	B1→2	14 ± 7.1	Transdermal	5 µg 17β-oestradiol/day
		B2→5	20 ± 11.6	Substitution	10 µg 17β-oestradiol/day
		B3→5	54 ± 26.3	Treatment	25 µg 17β-oestradiol/day

UTS = Ullrich-Turner syndrome; 17β-oestradiol = 17β-oestradiol; f = female; m = male; DES = diethylstilboestrol; INH = isonicotinic acid hydrazide; UE = urinary oestrogens.

puberty secondary to non-classic 21-hydroxylase deficiency (Speiser, 1995)

Gonadotrophin-independent precocious puberty

An overview of the various aetiologies is shown in Table II. Gonadotrophin-independent precocious puberty can originate from the gonads, the adrenals, from extragonadal or intragonadal sources of human chorionic gonadotrophin, or from exogenous sources. The majority of cases of gonadotrophin-independent precocious puberty are permanent; however, in some instances it also may be transient (e.g. autonomous ovarian cysts with self-limiting activity).

Gonadotrophin-independent isosexual or heterosexual precocious pseudopuberty due to suspected or proven oestrogen exposure

In prepubertal children, increased oestrogen intake or exposure may lead to precocious pubertal development which is isosexual in girls and heterosexual in boys. Main symptoms are breast development, hyperpigmentation of areolae, of linea alba, genitals and skin folds, and in girls, in addition, vaginal discharge and menstruation. The first cases described were due to diethylstilboestrol (DES) exposure (Hesselvik, 1952; Prouty, 1952; Cook *et al*., 1953; Green, 1958; Weber *et al*., 1963; Landolt and Mürset, 1968; Halpérin and Sizonenko, 1983; Table I). Routes of incorporation were transdermal (Hesselvik, 1952; Prouty, 1952;

Table V. Potential contamination of meat with 17β-oestradiol (ng steroid hormone per kg tissue)

Animal	Content of 17β-oestradiol found in animals (ng/kg tissue)		
	Muscle	Liver	Fat
Calf, untreated	0.11 ± 0.14	0.07 ± 0.16	0.13 ± 0.06
Cow, pregnant	32.7 ± 16.1	1027 ± 365	67.6 ± 34.6
Heifer, treated[a]	10.7 ± 5.1	3.2 ± 2.4	49.3 ± 30.8

Data are given as mean ± SD.
[a]Treatment with implant containing 200 mg testosterone propionate and 20 mg oestradiol benzoate (Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, 1999).

Green, 1958; Landolt and Mürset, 1968; Beas *et al*., 1969; Ramos and Bower, 1969; Edidin and Levitsky, 1982; Halpérin and Sizonenko, 1983; Peter *et al*., 1995; Tiwary, 1998), oral ingestion (Cook *et al*., 1953; Green, 1958; Weber *et al*., 1963; Landolt and Mürset, 1968; Fara *et al*., 1979; Kimball *et al*., 1981), and even inhalation (Prouty, 1952). In some cases, however, the source of the exposure to exogenous oestrogen remained obscure (Kimball *et al*., 1981; Pasquino *et al*., 1982; Freni-Titulaer *et al*., 1986; Nizzoli *et al*., 1986). Over the years several additional cases resulting from substances other than DES have been reported (Table IV). In most cases children had come into contact with ointments, creams, hair tonics or tablets from other household members. Contamination of a prescription drug with DES due to a manufacturing problem (improperly cleaned tablet-making machine) caused a small outbreak of precocious pseudopuberty in two hospitals (Weber *et al*., 1963). Plasma oestradiol concentrations were highly variable. A low plasma oestradiol did not exclude oestrogen-induced development of secondary sex characteristics. Exposure to exogenous oestrogens has to be ruled out with great care to avoid unnecessary laparotomy (Cook *et al*., 1953). The importance of the topic of oestrogen contamination has been confirmed by the finding of a high usage frequency of hair care products which contained oestrogens (7.8%) in a series of 102 children with sexual precocity (Zimmerman *et al*., 1995), and by a report on four girls using hair products which contained hormones or placenta (Tiwary, 1998). These authors pointed out the importance of extremely thorough questioning of the parents and of actually looking at the labels and the products used in the patients' homes. The dose of oestrogen the children were exposed to could not be determined in most cases (Table IV). However, a maximal daily exposure to 330 µg oestradiol was suspected (Peter *et al*., 1995). For comparison, the induction of puberty in girls with Ullrich-Turner syndrome can be achieved by the transdermal administration of increasing doses of 5-25 µg 17β-oestradiol/day (Illig *et al*., 1990). It is therefore not surprising that the girl with the oestrogen exposure to 330 µg/day showed all signs of precocious puberty including bone age acceleration (Peter *et al*., 1995). However, it must be stressed that in contrast to patients with congenital adrenal hyperplasia, familial male-limited precocious puberty or McCune-Albright syndrome, no patient has been reported in whom secondary central precocious puberty developed after precocious pseudopuberty due to exogenous oestrogen exposure.

Two epidemics of premature onset of puberty are of particular interest. The first was noted at Italian schools between 1977 and 1979 (Fara *et al*., 1979; Scaglioni *et al*., 1978). An apparent outbreak of breast development involving several hundred children was seen at a school in Milan (Fara *et al*., 1979; Scaglioni *et al*., 1979). Plasma oestradiol concentrations were slightly elevated. The clinical picture was mild; usually breast enlargement was Tanner stage 2. A source of oestrogen was not identified, however, the uncontrolled supply of poultry and veal putatively contaminated with oestrogens was suspected to be the origin of the problem (Fara *et al*., 1979). In Italy a surprisingly high number of baby food made of homogenized veal was found to have oestrogenic activity and to contain DES (Loizzo *et al*., 1984). However, the number of contaminated baby food samples decreased to zero between 1980 and 1982. As older children were also affected, the contamination of baby food could not explain the whole epidemic. A surprisingly high prevalence of premature thelarche (21.1% of 1-2 year old girls) and gynaecomastia (36.6% of 1-2 year old boys) was found in northern Italy (Nizzoli *et al*., 1986). The highest numbers were reported from Milan. However, statistical analysis did not show a significant factor associated with the clinical signs.

The second, even larger, epidemic was reported from Puerto Rico (Pérez Comas, 1982). Initially, more than 500 children were examined over a 7 year period for signs of precocious pubertal development (Pérez Comas, 1982; Saenz de Rodriguez *et al*., 1985). The majority presented with premature thelarche, but a considerable number ($n = 158$) showed additional signs of maturational advancement (Saenz de Rodriguez *et al*., 1985). Food contamination with oestrogenic substances—the first suspect was DES—and with naturally occurring phyto-oestrogens have been implicated as causing the epidemic (Schoental, 1983). However, to date, no single substance was found in food samples. In a case-control study, significantly positive associations were found for children below 2 years old between premature thelarche and the consumption of soy-based formula and of various meat products (Freni-Titulaer *et al*., 1986). However, in more than 50% of the case subjects, no exposure to any of the risk factors was present. Thus, the value of the statistical analysis remained questionable. Furthermore, a dose-response effect was not taken into account (Montague-Brown, 1987). In a recent status report from Puerto Rico (Perez-Comas *et al*., 1991) more than 3000 cases were collected. Although the results of clinical and laboratory studies and the protective effect of certain diets provided evidence for an oestrogenic contamination of food, no defined substance could be identified to date.

Food contamination with oestrogens as a cause of precocious pseudopuberty?

The Italian and Puerto Rican precocious puberty epidemics have drawn attention to the question as to whether the induction of precocious puberty is theoretically possible by the ingestion of oestrogen-contaminated meat or meat products. What is an acceptable and safe intake of oestrogens from exogenous sources for children? A guideline from the US Food and Drug Administration defines an additional intake of not more than 1% of the normal daily oestrogen production rate of prepubertal children as safe (US Food and Drug Administration, 1999). Thus, the calculation of the excess daily oestrogen intake depends on the

Table VI. Excess dietary intake of 17β-oestradiol (ng/person per day) calculated on the basis of a standard diet consisting of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat per day (Joint FAO/WHO Expert Committee on Food Additives, 1988a,b)

Excess intake with WHO/JECFA standard diet (ng/person/day)	
Bull, treated	-1.0 to +0.9
Ox, treated	-0.4 to +47
Heifer, treated[a]	+2.8 to +6916
Cow, pregnant	+465
Calf, treated[b]	+4753 to +4783
Estimated intake for a child (ng/100 g meat/day)	
Calf, untreated	3–11
Calf, treated[b]	1600
Heifer, untreated	0–3
Heifer, treated[a]	0.6–1010
Ox, untreated	0.1–0.7
Ox, treated	1–6
Worst case scenario = total steroid implant in one jar of baby food	20 mg oestradiol benzoate

In the lower half of the table, 17β-oestradiol intake calculated for a child with the daily consumption of 100 g muscle meat is shown (minimal and maximal values).
[a]Treatment with implant containing 200 mg testosterone propionate and 20 mg oestradiol benzoate.
[b]Treatment with implant containing 200 mg testosterone and 20 mg 17β-oestradiol (Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, 1999).

normal daily oestrogen production rate for prepubertal girls and boys. This was reported to be 6 µg 17β-oestradiol per day for prepubertal boys (Joint FAO/WHO Expert Committee on Food Additives, 1988a). However, this estimate has been criticized regarding the relatively insensitive methods for the measurement of plasma oestradiol and the calculation of the oestradiol production rate (Andersson and Skakkebaek, 1999). A revised calculation on the basis of a new ultrasensitive oestradiol recombinant cell bioassay (Oerter-Klein *et al*., 1994) and using an adapted metabolic clearance rate for children showed a much lower daily oestradiol production rate of 0.04 µg/day (Andersson and Skakkebaek, 1999). According to the US Food and Drug Administration guidelines, the acceptable exposure to oestradiol through food would thus be 0.43 ng/day in boys and 3.24 ng/day in girls.

The excess oestradiol intake will depend on the steroid concentration in meat. A review of steroid concentrations in meat of untreated and of steroid-treated cattle showed a large variability of concentrations, the highest oestradiol tissue concentrations being found in pregnant heifers (Joint FAO/WHO Expert Committee on Food Additives, 1988a,b; Scientific Committee on Veterinary Measures Relating to Public Health, 1999). Furthermore, methodological questions with respect to the measurement of steroids in meat remain open. These limitations notwithstanding, the concentration of oestradiol in meat may be as low as 0.11 ng/kg muscle in untreated calves or as high as 1027 ng/kg liver in pregnant cows (Table V). Calculation of the intake of oestradiol through meat on the basis of a standard diet (Joint FAO/WHO Expert Committee on Food Additives, 1988) revealed that the excess dietary intake can be negligible or substantial (e.g. up to 6916 ng/person/day), depending on the type of steroid treatment and on the animal used (Table VI). The manufacturing process of meat products has no influence on the structure and concentration of steroid hormones present in animal tissues (Fritsche and Steinhart, 1999; Karg and Meyer, 1999) and is therefore no safeguard against oestrogen ingestion. The estimated daily consumption of 100 g meat (calculated for muscle) may result in an intake of a maximum of 1600 ng oestradiol per day in a child (Bergner-Lang *et al*., 1989; Table VI). This intake would clearly be in excess of the FDA guideline. The worst-case scenario of a complete hormone implant finding its way into a jar of baby food leads, of course, to an exorbitantly high oestrogen exposure. Thus, it seems possible for children to be exposed to a significant amount of oestrogens through food consumption. However, in order to cause precocious pseudopuberty, this exposure would have to be constant over a time period of some months, which is very unlikely. To our knowledge, there are no reports in the literature showing that precocious pseudopuberty was the consequence of a proven exposure to oestrogen in food. The signs that might be expected from a moderate but prolonged oestrogen exposure are other than precocious puberty and have been reviewed recently (Andersson and Skakkebaek, 1999). Although there is concern that oestrogen consumption through food might have adverse effects on pubertal development and even human health, there are no published data to support the notion that an increased overall exposure to environmental oestrogens has led to an increased incidence in precocious puberty or to an earlier start of pubertal development.

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