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., 1987). 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; Cnosse 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 meningo(myelo)coele 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).

Pathophysicsiology

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
The differences in differential diagnoses (Tables I and II) and puberty and the peripheral types of precocious puberty because of medical treatment of central precocious puberty by long-acting GnRH agonistic analogues is irrespective of the aetiology. 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, 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 peripheral type of 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., 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; 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).
Pathogenesis of precocious puberty

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

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

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., 1997; 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).
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 pubert...
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 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; Halperin 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)

<table>
<thead>
<tr>
<th>Animal</th>
<th>Content of 17β-oestradiol found in animals (ng/kg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Muscle</td>
</tr>
<tr>
<td>Calf, untreated</td>
<td>0.11 ± 0.14</td>
</tr>
<tr>
<td>Cow, pregnant</td>
<td>32.7 ± 16.1</td>
</tr>
<tr>
<td>Heifer, treated</td>
<td>10.7 ± 5.1</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD.

*Treatment with implant containing 200 mg testosterone propionate and 20 mg oestradiol benzoate (Bundesinstitut für Gesundheitliche Verbraucherschutz und Veterinärmedizin, 1999).

Green, 1958; Landolt and Mürset, 1968; Beas et al., 1969; Ramos and Bower, 1969; Eddin 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 oestriadiol concentrations were highly variable. A low plasma oestriadiol 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 oestriadiol 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-oestriadiol/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 oestriadiol 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 (Schoenthal, 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 (Pérez-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
Pathogenesis of precocious puberty

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
- Ox, treated
- Heifer, treated
- Cow, pregnant
- Calf, treated

Estimated intake for a child (ng/100 g meat/day)

| Calf, untreated | 3–11 |
| Calf, treated  | 1600 |
| Heifer, untreated | 0–3 |
| Heifer, treated  | 0.6–10 |
| 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).


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