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Endocrine disrupters and possible contribution to pubertal changes

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The onset of puberty strongly depends on organizational processes taking place during the fetal and early postnatal life. Therefore, exposure to environmental pollutants such as Endocrine disrupting chemicals (EDCs) during critical periods of development can result in delayed/advanced puberty and long-term reproductive consequences. Human evidence of altered pubertal timing after exposure to endocrine disrupting chemicals is equivocal. However, the age distribution of pubertal signs points to a skewed distribution towards earliness for initial pubertal stages and towards lateness for final pubertal stages. Such distortion of distribution is a recent phenomenon and suggests environmental influences including the possible role of nutrition, stress and endocrine disruptors. Rodent and ovine studies indicate a role of fetal and neonatal exposure to EDCs, along the concept of early origin of health and disease. Such effects involve neuroendocrine mechanisms at the level of the hypothalamus where homeostasis of

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reproduction is programmed and regulated but also peripheral effects at the level of the gonads or the mammary gland.

Introduction

Puberty represents a crucial milestone in one's reproductive life. For this reason, any effect of the environment on pubertal timing might announce later consequences on reproduction. For the last 20 years, data has accumulated suggesting changes in pubertal timing and a possible role for exposure to endocrine disrupting chemicals (EDCs). This review will summarize the recent data regarding secular trends in age at puberty in boys and girls as well as the likely increase in central precocious puberty incidence in girls. Finally, we will review the epidemiological and animal data suggesting a role for endocrine disrupting chemicals in the reported changes in pubertal timing.

Secular trend in pubertal timing in girls

Because menarcheal age and breast development are clinically easier to assess, data regarding female puberty is significantly more abundant than male data.

A reduction in menarcheal age had been reported in European countries [1] as well as in the United States [2] between 1890 and 1960. An overall advancement in female pubertal timing that averaged 4 years in a century was derived from those observations [2]. This evolution is considered to be due to the improvement of socioeconomic conditions and nutritional status. The hypothesis is consistent with the Frisch and Revell theory according to which a critical amount of body fat is necessary in order to enter puberty [3]. Since 1960, the secular advancement in menarche has appeared to cease in countries such as Belgium [2,4]. In the United States, menarcheal age remained stable, around 12.7–12.9 years, between 1973 and 1997 [5–7] but a recent longitudinal study has reported a slightly lower median age at menarche (12.2 years) in New-York, Ohio and California [8]. A similarly moderate decrease in age at menarche was reported in Danish cohorts between 1991 and 2006 (13.42 and 13.13 years, respectively) [9]. Interestingly, a stronger secular decrease persists in emerging countries such as India or China [10,11]. However, an extensive spatial heterogeneity regarding age at menarche still persists in those regions of the world.

Starting in the nineties, several large US studies have reported a persistent secular decrease in age at onset of breast development in girls compared to the mid-20th century. A publication from the American Academy of Pediatrics reported a mean age at B2 of 10 years in White American girls and 8.9 years in African-American [7]. These findings generated comments on the possible overestimation of breast development because assessment was made through visual inspection only, whereas palpation may be required to distinguish between adipose and glandular tissue. The Third National Health and Nutrition Examination Study (NHANES III), a population-based study conducted between 1988 and 1994, confirmed the findings and found the median age of thelarche to be 10.4 years in white Americans and 9.5 in black Americans [12]. Following those observations, in 2007, an expert panel stated that the data were sufficient to suggest a trend toward earlier breast development in the United States over the second half of the 20th century [13]. A more recent longitudinal study by Biro et al. observed a continuous decrease in age at B2 in American girls aged 6–8 years at enrollment [14]. Mean age of breast stage 2 was 8.8 years for black, 9.2 years for Hispanic, 9.6 for non-Hispanic white, and 9.9 years for Asian participants, illustrating the influence of race/ethnicity on breast maturation. Notably, body mass index had a greater effect on age at menarche than did race and ethnicity. Those data are consistent with data collected in Scandinavian countries: The Copenhagen Puberty Study reported an advance of nearly one year for attainment of Tanner stage 2 between girls from the 1991 cohort and girls from the 2006 cohort [9]. Recent European studies have also highlighted the existence of a non-Gaussian distribution of the age at B2 in girls with a distribution skewed to the left, meaning that more girls start puberty early than late. A recent longitudinal study in Greek girls showed a median age at B2

of 10 years with the 25th and 75th centiles being 9.2 and 10.6 years, respectively and a skewness of −0.44 [15]. Cross-sectional data in Belgium [4] were consistent with those findings: the distribution of age at B2 was skewed towards earliness whereas the distribution for age at menarche was skewed towards lateness. The negative distortion of age at B2 appears to be more marked in recent studies [4]. These observations suggest that during the last decades of the 20th century, some girls tended to enter puberty earlier and some to end puberty later, which was not reflected by changes in median ages. Very recently, Woelfle et al. assessed secular trends on pubertal development in more than 7000 patients with Turner syndrome [16]. They found a decline in the age at spontaneous thelarche of about 2 years between those born before 1980 and those born in 2000–2004. The prevalence in spontaneous puberty onset appeared to increase between 1980 and 1995–1999. As in healthy girls, one can speculate that the increase in weight SDS and exposure to EDCs explains such secular trend in pubertal timing.

The secular changes in age at pubertal onset and changes in distribution pattern indicate a potential role for environmental factors. However, the causal relationship is extremely difficult to establish. When searching for possible causes and mechanisms of changes in pubertal timing, the default hypothesis is hypothalamic-pituitary maturation. Peripheral mechanisms, however, can coexist with central mechanisms or secondarily facilitate them. Such a concept is supported by the dissociation between advancement in age at onset of breast development in Denmark, the Netherlands, Belgium or the United States without parallel change in menarcheal age. Two different pubertal events can respond differently to hormonal and EDC influences. Moreover, a single pubertal event can be influenced by different endocrine pathways. For instance, breast development can be due to ovarian estrogen secretion under the stimulation by pituitary gonadotropins and/or estrogenic effects associated with exposure to EDCs. The interpretation of the mechanistic role of sex steroids or related environmental factors is complex due to the multiple sites where they can interact between the hypothalamus and the peripheral target tissues. Interestingly, there was no difference in serum follicle stimulating hormone and luteinizing hormone between the two Danish cohorts in 1991 and 2006 which would suggest that the change in timing of breast development would not result from an early activation of the pituitary-gonadal axis. However, multiple animal models indicate that early exposure to EDC can alter the hypothalamic programming of puberty (see below).

The role of the obesity epidemics in puberty timing deserves to be developed as well. Because nutritional status is known to be a determinant of puberty, a causal relationship between obesity and earlier onset of puberty has been hypothesized. Evidence has accumulated that a sufficient amount of fat mass signaling to the neuroendocrine system through leptin is a prerequisite to the onset of puberty. Leptin can stimulate pulsatile gonadotropin-releasing hormone (GnRH) secretion and is indeed necessary but not sufficient to account for onset of puberty [17]. It also appears that both energy balance and pubertal timing share common regulatory factors that could be jointly influenced. Notably, in Biro's study, body mass index (BMI) was the strongest predictor of earlier age at breast development [8]. In their study, white non-Hispanic participants with BMI <85th percentile had similar age at breast development as white girls in 1997 [7], indicating that the secular trend had plateaued in that group. Other studies have suggested an association between body weight and puberty timing. Adiposity rebound (BMI increase between 2 and 8 years) has been linked with earlier growth spurt in Danish boys and girls [18]. Aksglaede et al. have found that BMI at 7 years is a significant predictor of age at pubertal growth spurt in a cohort of more than 150,000 boys and girls [18]. However, secular trend towards early onset of puberty is found in all BMI categories suggesting involvement of other factors than peripubertal weight.

Secular trend in pubertal timing in boys

Pubertal timing in boys being relatively more difficult to assess, the number of available studies is significantly lower. In the 1990s, data collected from the American population-based study NHANES III suggested an advance in age at onset of genital development [12,19,20]. However, due to the lack of reliable data from the previous population based study NHESIII [21], no conclusions could be made regarding the trend in pubertal onset in boys. Only a limited number of secular trend studies exist in Europe, and they did not support a secular trend toward earlier age at pubertal onset in boys between the 1960s and the 1990s [22,23]. Recent data collected in Scandinavian countries are consistent with an

earlier pubertal timing: the age at attainment of testicular volume above 3 ml was about 3 months earlier in the 2006–2008 cohort compared to the 1991–1993 cohort [24]. Significantly higher LH, but not testosterone, levels were found in 2006–2008 compared to 1991–1993 and BMI Z-score increased significantly from 1991 to 1993 to 2006–2008. However, pubertal onset and LH levels were no longer significantly different between study periods after adjustment for BMI.

Recently, the Puberty Cohort in Denmark (2012–2017) has reported a mean age at Tanner Stage 2 of 11.1 years [25] corresponding to an advance of around half a year compared to the previous Danish cohort [24]. Interestingly, age at pubertal endpoint (Tanner stage 5) was similar. It is important to note that the methods for data collection differed, making the comparison between the two studies difficult: the first study used clinical examination whereas the second one used questionnaires with self-reported information on Tanner stages. Another milestone of male puberty, voice break, has been reported to advance as well. The Puberty Cohort in Denmark (2012–2017) reported an average age of 13.1 years, which is considerably earlier than former studies reporting between 15.5 and 14.0 years in the period 1968 to 2005 [26,27]. Here again however, the evaluation methods differ, rendering comparison difficult to conduct.

As already pointed out in girls, the initial pubertal signs and signs of completion of puberty appear to show divergent secular changes, suggesting heterogeneity in response of pubertal events to modulating factors. As an example, the first 3–10% of boys with evidence of initial pubertal increase in testicular volume ($\geq$4 ml) are younger than in the past (reviewed in 4), whereas the final 3–10% (centile 90 and 97) appear to attain adult testicular volume ($\geq$15 ml) later (reviewed in 4).

Is prevalence of precocious puberty increasing?

Data regarding the prevalence of precocious puberty and the existence of a secular trend is very scarce. In 2005, an epidemiological study based on national registries in Denmark estimated that 0.2% of Danish girls and <0.05% of Danish boys had some form of precocious pubertal development [28], which was much higher than data from 40 years ago [29]. However, the overall prevalence could be overestimated because precocious pubertal development included patients with true central precocious puberty as well as patients with premature adrenarche and premature thelarche. Moreover, the age limit of 8 years and 9 years for diagnosis of sexual precocity in girls and boys respectively was extended to 9 and 10 years. Several years later, another study in Denmark found an increase in the number of girls referred for early pubertal development between 1993 and 2009 [30]. In this cohort of 449 Caucasian girls, 88 girls (19.6%) were diagnosed with central precocious puberty (breast development before 8 years and LH peak in the LHRH test > 5 U/L or LH/FSH ratio > 0.66 or basal LH > 0.3 U/L) and only six with peripheral precocious puberty. It follows that more than 50% of the girls referred for advance of pubertal development had no true precocious puberty but conditions that need only a follow up without treatment (Tanner Breast 2 between 8 and 9 years, premature thelarche or premature adrenarche). Another report from tertiary care centers with pediatric endocrinology in Spain estimated a lower incidence compared with Danish data since the prevalence for girls was 0.037% and <0.0005% for boys [31].

European data seem to be consistent with observations in other part of the world such as in Korea. In an epidemiologic study using a national registry, the annual incidence of central precocious puberty increased steeply, in particular, among girls between 2004 and 2010 [32].

Interestingly, this increase in central precocious puberty appears to be more marked in girls than boys [31–33] which could suggest a greater sensitivity of female subjects to environmental factors.

Pubertal timing and EDC exposure in humans

Except in conditions such as industrial spills resulting in accidentally high exposure of a given population to a given EDC, demonstrating the effects of endocrine disruptors on pubertal timing in human conditions remains difficult for several reasons. Girls and boys entering puberty are exposed to low doses of hundreds of chemicals, rendering causation difficult to demonstrate. The exposure may have taken place during the prenatal or the early postnatal period leading to a long latency between exposure and the potential consequences on pubertal timing. Moreover, the effects of exposure to

endocrine disruptors can differ depending on the studied endpoint (i.e. breast development or menarche).

The possible involvement of early life exposure to endocrine disruptors on pubertal timing has been suggested by the observation that the risk of sexual precocity was 80 times higher in children migrating to Belgium for international adoption compared to Belgian native children. Those children had been formerly exposed to the estrogenic insecticide dichlorodiphenyltrichloroethane (DDT) in the country of origin [34]. Vasiliu et al. [35] have also reported early menarche after presumable prenatal/early postnatal exposure to dichlorodiphenyldichloroethylene; a metabolite of DDT. In Denmark, similar findings have been reported in the daughters of women exposed to pesticides due to occupation in green houses [36]. Prenatal exposure to pesticides very early during gestation was associated with earlier breast development in girls. This association appeared not to be caused by changes in gonadotropins, but rather to higher androgen levels, which indirectly may increase oestrogens through aromatization. Studies focusing on the effects of soy-based infant formula on pubertal development have led to mixed results. Most studies are retrospective and limited in term of participants. Some studies have reported that age at menarche appeared to be earlier in girls fed with soy products during infancy [37,38]. In a contemporary British cohort, *in utero* exposure to phytoestrogens was associated with changes in age at menarche with opposite effects depending on the measured phytoestrogen [39]. Prenatal exposure to flame retardants such as polybrominated diphenyl ethers (PBDEs) has been associated with later age at menarche [40] while the National Health and Examination Survey (NHANES) showed that higher serum PBDE concentrations between ages 6 and 8 years [41] or 12 and 19 years [42] was associated with slightly earlier menarche or older age at onset of breast development respectively, illustrating once more the potential importance of the window of exposure and sensitivity.

Data about effects of early exposure to endocrine disruptors on pubertal timing in boys are sparse and sometimes contradictory. In 2005, Hsu and colleagues reported a decrease of testosterone levels and increase in FSH levels in chinese boys of mother accidentally exposed to high doses of polychlorinated biphenyls/polychlorodibenzofuranes by ingestion of rice oil contaminated by those compounds [43]. In a birth cohort from the Faroe Islands, prenatal exposure to PCB was associated with lower serum concentration of LH and testosterone [44]. However, only the neonatal levels were predictive of slightly smaller testes [44]. Those results were similar to those described by Eskenazi and colleague [45] in the CHAMOCOS cohort: lower LH and testosterone values were observed in boys of mothers with higher maternal DDT levels. Concomitantly lower LH and testosterone levels in serum suggested a central origin of delayed puberty.

Mechanisms of changes in pubertal timing caused by EDCs

The secular trend in age at onset of puberty as well the possible increased incidence in central precocious puberty in girls suggest a role for environmental factors, EDCs in particular. However, these epidemiological findings in humans face limits as far as clarification about which chemical is involved, which age window is critical, and where the mechanisms take place in the hypothalamic-pituitary-gonadal axis. Therefore, human studies need to be complemented by studies using animal models.

It appears that the programming of pubertal maturation is an adaptive mechanism responding to environmental factors very early on. In primate and ovine species, pubertal timing is sexually dimorphic, and sex steroids play a crucial role in gender differences in pubertal timing. Thus it appears logical that early alteration of sex steroid action could affect the programming of puberty timing. The effects of environmental changes or stressors on pubertal timing depend on the period of occurrence or exposure. For instance, prepubertal underfeeding leads to delayed puberty; overfeeding and excess of adiposity in humans may lead to early puberty, whereas intrauterine growth restriction is associated with early puberty (reviewed in 4). What do rodent models teach us regarding critical periods of sensitivity to EDCs? In female rats, for instance, the effect of bisphenol A on pubertal onset appears to depend on the timing of exposure. Vaginal opening is unchanged after gestational exposure, whereas early postnatal exposure is followed by early puberty [46]. Exposure of male rodents to EDCs such as DDE [47], vinclozolin [47] or diethylstilbestrol [47,48] leads to delayed puberty after postnatal exposure (postweaning) as opposed to absence of effects after prenatal exposure (reviewed in 4). The

developmental variations in rodents' sensitivity to EDCs, however, cannot be strictly extrapolated to the critical periods in humans on the account of possible differences between species.

The interpretation of the mechanisms of action of environmental factors is complex due to the multiple sites where they can interact between the hypothalamus and the peripheral target tissues. Abnormal pubertal development caused by EDCs may result from alterations taking place at different levels: the hypothalamic GnRH network, the gonadotropic cells or the gonads themselves (Fig. 1). The physiological acceleration of GnRH secretion before puberty in rat hypothalamic explants can be used to study the effects of environmental factors on the hypothalamic control of puberty [49–52]. In order to model early exposure of migrant children to the pesticide dichlorodiphenyltrichloroethane (DDT), neonatal female rats were exposed to DDT from postnatal day 6–10. Such exposure led to advanced acceleration of pulsatile GnRH secretion and early onset of puberty [53]. The effect involved estrogen receptors, the dioxin/aryl hydrocarbon receptor (AhR) and a subtype of glutamate receptor [54,55]. Using the same model, we showed that neonatal exposure to an environmentally relevant dose of BPA (25 ng/kg/d) for 15 days was followed by a delay in developmental reduction of GnRH interpulse interval studied *ex vivo* on postnatal day 20. In contrast, exposure to BPA 5 mg/kg/d for 15 days resulted in a premature reduction in GnRH interpulse interval and a trend toward early vaginal opening [56]. Notably, the very low and environmentally relevant dose of BPA delayed neuroendocrine maturation related to puberty through increased inhibitory GABAergic neurotransmission [56]. Recent studies have shown that other members of the GnRH network could be targeted (Fig. 1). The ontogeny and function of kisspeptin neurons are profoundly influenced by gonadal steroids and vulnerable to endocrine disruption [57]. In addition, alterations of sensitivity to sex steroids in sexual dimorphic regions of the hypothalamus can have long-lasting consequences on the control of puberty and reproduction. It has been shown that EDC can affect the expression of estrogen receptors and alter the sensitivity of specific brain regions to endogenous estrogens [58] or polybrominated diphenyl ether-99 [59] and, by consequence, may alter GnRH secretion. EDCs can also interfere with the physiological (prominently inhibitory) feedback mechanisms of sex steroids in hypothalamic-pituitary function, while they can also act as a primer of neuroendocrine maturation [55]. Finally, they can interfere with hormones at the level of peripheral target tissues. Breast development could result from estrogenic EDC effects independent of the hypothalamic-pituitary maturation. This dissociation of effects on breast development and menarche could account for the secular reduction in the correlation coefficient between the ages at occurrence of the two pubertal events reported by some authors [60].

Recent data has shown that female puberty is controlled by epigenetic mechanisms such as histone modifications, DNA methylation and non-coding RNA [61]. Environmental factors such as EDCs affect epigenetic regulation in several tissues but studies identifying how epigenetic pathways convey information from EDCs to hypothalamic neurons regulating the onset of puberty are still required.

Summary

Recent data have shown a persistent secular trend toward early pubertal onset in girls and boys. Detailed analysis actually reveals that the pattern of age distribution is affected. Current variations in pubertal timing involve a trend towards negative or positive distortion for initial or final pubertal stages, respectively, both in girls and boys. This suggests some heterogeneity in response of pubertal events to modulating factors. Those subtle changes are important in clinical practice since the extreme lower and upper age limits in the normal population are used to define early or late maturation. Relatively scarce data suggest that the incidence of central precocious puberty is increasing as well. This trends appears more marked in girls, which again suggest a sexual difference in sensitivity to environmental factors.

The changes taking place in the borderline physiological timing of puberty can be of clinical relevance due to behavioral consequences. Early puberty has been shown to be associated with more frequent adolescent risk taking behaviors and with psychopathologies persisting throughout adult life [62–65]. These issues may account for a significant impact on both the clinician and the society. In addition, altered puberty timing can be a marker of subsequent reproduction abnormalities later in life. In the long term, early and precocious timing of puberty also predict a slight but significant increase in the risk of breast cancer [66], angina, hypertension and type 2 diabetes [67].

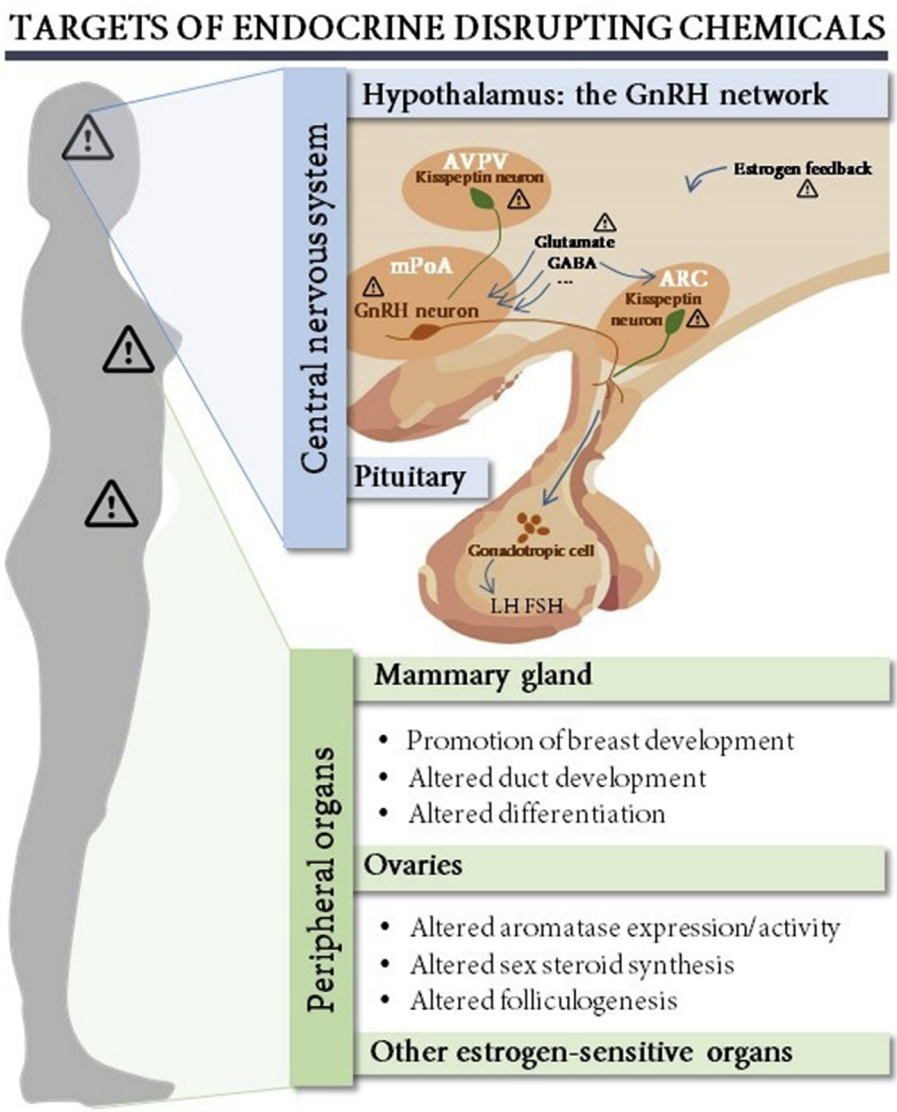

Fig. 1. Schematic representation of EDC targets potentially involved in alterations of pubertal development. Abnormal pubertal development caused by EDCs may result from disruption taking place at different levels: the hypothalamic GnRH network, the gonadotropic cells, the gonads themselves or the mammary gland. ⚠ represent the potential targets of EDCs as identified by animal studies.

Epidemiological and animal studies have shown that the programming of puberty and reproduction is very sensitive to exposure to EDCs. Both hypothalamic and gonadal targets have been identified. However, the Organisation for Economic Co-operation and Development currently recommends to use the postnatal days 22–42 as validated exposure period for EDC testing. Those guidelines ignore the earlier period that is critical for neuroendocrine maturation, particularly the developmental acceleration of pulsatile GnRH secretion and miss the concept that pubertal timing can be influenced long before the period immediately preceding the onset of puberty. Moreover, in recent years it has been shown that female puberty is controlled by epigenetic mechanism as histone modifications, DNA

methylation and non-coding RNA. Epigenetic repression and activation of gene transcription is a core mechanism by which epigenetics regulates pubertal development. EDCs can affect epigenetic regulation in several tissues and may convey information from a wide range of stimuli to hypothalamic neurons regulating the onset of puberty.

Practitioners can play an important role in both collecting and providing information about the potential burden of EDCs. They should be involved in the promotion of a consumer behavior reducing that burden because puberty is only one among several health issues related to EDCs such as abnormal sexual differentiation, neurodevelopmental diseases, metabolic syndrome and increased risk of neoplasia.

Conflicts of interest

The authors have no conflict of interest to declare.

Practice points

- Age distribution of pubertal signs points to a skewed distribution towards earliness for initial pubertal stages and towards lateness for final pubertal stages. It is thus very important to take both the beginning and end of puberty into account when evaluating secular trend in pubertal timing.
- Recent data indicate an increased incidence of central precocious puberty but this data requires larger epidemiological studies.
- Measurement of EDC exposure in individual patient with precocious puberty cannot be interpreted reliably. However, the practitioner can play an important role in collecting data regarding the potential burden of EDCs or the documentation of an epidemics of abnormal puberty in a given region.
- The clinician can play an important role in the promotion of a consumer behavior reducing EDC burden in the pregnant woman and child.

Research agenda

- The effects of EDC mixtures on the control of puberty and reproduction need to be explored further.
- Recent data indicate that EDCs can affect puberty and reproduction transgenerationally. These concerning effects need to be investigated.
- Potential changes in central precocious puberty (especially in girls) incidence need to be documented.

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