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MiniReview

Endocrine Disruptors and Abnormalities of Pubertal Development

Greet Schoeters[1,2], Elly Den Hond[1], Willem Dhooge[4], Nik van Larebeke[3] and Marike Leijs[5]

[1]Vlaamse Instelling voor Technologisch Onderzoek (VITO), Environmental Toxicology Unit, Mol, Belgium, [2]Department of Biomedical Sciences, University of Antwerp, Wilrijk, Belgium, [3]Study Centre for Carcinogenesis and Primary Prevention of Cancer, Department of Radiotherapy, Nuclear Medicine and Experimental Cancerology, Ghent University Hospital, Ghent, Belgium, [4]Department of Internal Medicine (Endocrinology), Ghent University Hospital, Ghent, Belgium, and [5]Ecobaby Foundation and Emma Children's Hospital, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

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Abstract: Onset and development of puberty is regulated by the neuroendocrine system. Population-based studies worldwide have observed secular trends towards earlier puberty development. These changes are apparently caused by environmental factors such as improved socio-economic status, improved health care and nutrition. However, they may also partly result from endocrine-disrupting chemicals in the environment. Epidemiological studies have investigated the relationship between pubertal development and exposure to endocrine-disrupting chemicals (polychlorinated biphenyls, polybrominated biphenyls, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, phthalate esters, furans and the pesticide endosulfan). Associations with both perinatal and postnatal exposure have been reported. Studies in experimental animals support some of these findings and point to differential endocrine regulatory mechanisms linked to pubertal development acting in the perinatal and the pre-pubertal period. Pubertal development is naturally associated with growth and body composition. There is increasing evidence for a link between prenatal development and pubertal onset. In girls born small for gestational age (SGA), pubertal onset and age at menarche often are advanced, especially if there has been an extensive catch-up growth during the first months of life. *In utero* growth retardation may have multiple causes including exposure to xenobiotic substances as was suggested for some endocrine-disrupting chemicals. An abnormal perinatal environment of children born SGA may alter the endocrine status and the sensitivity of the receptors for endocrine and metabolic signalling that may have effects on maturation of brain and gonads. However, the causal pathways and the molecular mechanisms that may link the pubertal growth pattern of children born SGA, pubertal development and endocrine-disrupting chemicals need further study.

Puberty is characterized by rapid physiological changes such as growth spurt and maturation of the gonads and the brain. It entails the individual's transition period from a non-reproductive to a reproductive state. Moreover, it is an acknowledged period of emotional stress and vulnerability to socio-environmental factors [1].

During the past decades, secular trends of earlier age at onset of puberty have been reported [2]. Not only may this increase the social burden due to a higher risk of pregnancies at early ages, changes in the timing of pubertal development may influence the risk for substance abuse, antisocial behaviour, eating disorders and emotional stress. Early sexual maturation in adolescents has been associated with a higher prevalence of alcohol and tobacco use in late adolescence [1]. This vulnerable period of transition into adulthood is fine tuned by endocrine-regulatory mechanisms [3].

Endocrine-disrupting chemicals have been implicated in numerous physiological processes affecting normal reproductive health in human beings and animals [4]. Monitoring changes in pubertal onset and development may function as early warning signs for reproductive capacity, both individually and at the population level. Therefore, this *MiniReview* will focus on environmental chemicals and what is known about their impact on puberty development in relation to critical windows of exposure.

Author for correspondence: Greet Schoeters, VITO, Environmental Toxicology Unit, Boeretang 200, Mol, B-2400, Belgium (fax +32 14333214, e-mail greet.schoeters@vito.be).

Secular trends in puberty onset and development

The physiological processes that regulate onset of puberty and transit through adolescence are not yet fully understood. Next to a genetic component, environmental factors are influencing timing of puberty onset [2]. While there seems to be a 4–5-year variation in 'normal' starting times for puberty among healthy children, the onset time varies between different ethnic groups. For example, puberty onset may occur between the ages of 8 and 14 in Caucasian girls, and may begin as early as 7 years of age in African-American girls. The average age of girls of the Kikuyu of Kenya to reach puberty onset was 13 years and the average age at menarche (first ovulation) was 15.9 years, which is much later than in the USA. African-American and Mexican-Americans girls are more likely than white girls to have

'early menarche', that is, menarche before 11 years. Asians are more likely than whites to mature later than 14 years [5].

The improvement of the nutritional and health status between mid-nineteenth century and the mid-twentieth century has been associated with an overall decrease in menarcheal age of an average 3 years in USA and in some countries of Western Europe [2]. This trend of decreasing age at menarche seems to have halted in most European populations although there are some reports describing further decreases in the US population [2]. The importance of the nutritional status has been demonstrated also in children migrating from developing countries. Danish studies showed that adopted children from developing countries have a 15–20-time higher risk of developing precocious puberty compared to Danish-born children [6]. Indian girls adopted by Swedish families had lower median menarcheal age than Swedish girls [7]. The nutritional status of these children changes upon arrival in the host country, which is followed by a catch-up in height and weight and precedes early sexual maturation. Earlier pubertal development was more pronounced in girls than in boys and the likelihood depended also on the age of adoption: precocious menarche (<10 years) being more common in Indian girls who arrived in Sweden between 3 and 6 years than in those who arrived before 2 years of age [7]. A relationship between pre-pubertal body mass index and the timing of puberty has been observed in retrospective studies in Denmark and in prospective studies in the USA [6,8]. However, whether the association is causative is not clear.

Markers for pubertal development

Puberty is a multifaceted process that may be monitored by different markers. External signs such as the development of breasts in girls, the increase in testicular volume in boys and pubic hair growth are staged in adolescents according to criteria defined in the pioneering work by Marshall and Tanner [9,10]. In girls, breast development, pubic hair growth, age at menarche and regular menstrual cycles are used as markers for pubertal development. In boys, the increase in testicular volume, pubic hair growth, spermaturia, age at first ejaculation, fundamental voice frequency, growth and height spurt and bone density are markers of puberty development [11]. The information on these markers can be collected non-invasively by health professionals or by self-assessment questionnaires [12]. However, interobserver variability may hamper the comparison of results among studies. Another complication is that the different physiological changes may be regulated by different triggers and may be not directly interconnected. Breast development ('thelarche', the onset of breast development) follows the secretion of ovarian oestrogen, whereas the development of female pubic hair ('adrenarche' or 'pubarche', the onset of pubic hair development) is caused by androgens from both the adrenal glands and ovaries. Oestrogen secretion and androgen secretion are controlled separately; thus, adrenarche and thelarche can occur in either a coordinated manner (which is the norm) or independently (which is rarer). Menarche occurs in response to the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that are released by the pituitary. Although menarche occurs generally in late puberty, about 2.0–2.5 years after breast budding, it is a singular event and many studies use menarche as a proxy for the onset of puberty. In boys, testicular enlargement and the secretion of testicular androgen (both are called 'gonadarche') usually, but not always, precede pubic hair development [13].

As onset of puberty and pubertal progression is under hormonal control, monitoring endocrine status may offer useful biomarkers of puberty. The main hormone involved in the regulation of puberty onset is gonadotropin-releasing hormone (GnRH) in the hypothalamus that stimulates release of both LH and FSH from the pituitary [3]. LH stimulates the production and release by the gonads of testosterone (boys) and oestrogens (girls) that can be measured in early puberty as elevated concentrations in morning urine samples [14]. The secretion of adrenal androgens starts in the earliest stages of puberty under control of the hypothalamus–pituitary–adrenal axis. These hormones cause pubic and axillary hair growth and sensitize the androgen receptors of the hypothalamus pituitary. Inhibins are peptides of gonadal origin that suppress FSH production. Inhibin B expression is high in infant boys but declines in concert with the increase in gonadotropins. In boys, serum inhibin B levels are markers of the maturation state of the Sertoli cells, they increase between Tanner stages 1 and 2, but then plateau [11].

Pre-pubertal changes in weight and height have been associated with puberty development, and thus it has been suggested that markers for energy balance and metabolic status may be early biomarkers for puberty development. More recently, leptin has been suggested to be the metabolic messenger between the fat cell and the hypothalamus that stimulates the onset of puberty [15]. Furthermore, insulin levels may stimulate hypothalamic neuronal cells to express and secrete GnRH [15].

The prevalence of precocious puberty has also been used as a marker for assessing pubertal development [16]. Precocious puberty has been defined in Europe as less than 8 years for the B2 Tanner stage in girls and less than 9 years for the G2 Tanner stage in boys. These age limits are below the first percentiles of the Gaussian distribution in the normal population. Precocious puberty is more frequent in girls than in boys. In most cases, precocious puberty is related to early hypothalamic pituitary maturation that is induced by gonadotropin and associated with increased LH secretion. In one-third to one-fifth of the cases, sexual precocity is related to increased secretion of adrenal or gonadal sex steroids or may be related to enhanced exposure to exogenous compounds [16]. In addition, delayed puberty may be a marker for abnormal puberty development. Delayed puberty is diagnosed when there is no breast development by 13.4 years of age in a girl and no testicular enlargement by 14 years in a boy [17]. Other markers that have been used are an increased delay between age at menarche and regular cycling.

Table 1.

Epidemiological studies investigating the relationship between perinatal exposure and pubertal development.

Compound	Study area	Study population	Methods	Main findings	Reference
DDE PCBs	Michigan angler cohort of fish eating mothers with serum DDE levels at time of pregnancy up to 25 µg/l	151 girls	Retrospective study Telephone interviews *In utero* exposure calculated from maternal serum levels	Reduced age at menarche by 1 year associated with an increase in *in utero* DDE exposure of 15 µg/l	[23]
DDE PCBs	North Carolina cohort with DDE concentrations up to 4 µg/g fat	316 girls 278 boys	Prospective study Mail questionnaires Concentrations in mothersmilk and maternal serum	No association with pubertal stages	[24]
PBBs	Michigan food chain contamination	327 girls	Prospective study Physical examination *In utero* exposure extrapolated from maternal serum levels at the time of the accident	Earlier age at menarche and earlier pubic hair stage in breastfed girls with *in utero* PBB exposure above 7 ng/g serum	[28]
PCBs	Faroese birth cohort	196 boys	Prospective study Clinical and physical examination Concentrations in cord blood	No effect on pubertal stages or testicular volume	[29]
PCBs PCDFs	Yucheng	55 boys	Prospective study Clinical and physical examination Maternal serum levels	Pubertal delay	[30]

DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; PBB, polybrominated biphenyl; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran.

Links with environmental pollution

Many reports have suggested a role of exogenous endocrine-disrupting chemicals in timing and development of puberty. Few epidemiological studies have addressed this hypothesis. These studies have been reviewed [18,19].

In many of these studies, timing of pubertal stages and menarche were self-reported. The size of the study populations varies also largely. Changes of pubertal development have been associated to perinatal dose (table 1) or to prepubertal dose (table 2). Doses are extrapolated from maternal serum concentrations or from serum concentrations at the time of accidental contamination.

In Belgium, high levels of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p′-DDE) were found in 26 immigrant girls (adopted and non-adopted) with precocious puberty [20]. The insecticide 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) can behave as an oestrogen agonist and its major metabolite p,p′-DDE has anti-androgen potency as shown by *in vitro* and animal studies [21,22]. In the so-called Michigan angler cohort, *in utero* exposure to high levels of DDE was associated with advanced age at menarche as measured in 151 daughters from fish-eating mothers compared to controls, polychlorinated biphenyls (PCB) having no effect on age at menarche [23]. The daughter's age at menarche and possible confounders were acquired by telephone interviews [23]. This finding was not confirmed in the North Carolina cohort in which self-reported age at menarche or pubertal stage in 316 girls and 278 boys was not associated with DDE [24].

Polychlorinated biphenyls have been described to display oestrogenic, anti-oestrogenic and anti-androgenic activities [25]. There are already several epidemiological studies that have assessed exposure to PCBs in relation to the timing of puberty. In a Belgian study comparing children (120 girls and 80 boys) from rural and urban areas, PCB congeners 138, 153 and 180 were measured in serum, and the pubertal stage was assessed by physicians [26,27]. No association of PCB levels to pubertal development in girls was observed, whereas in boys, a significant delay of puberty was found in urban areas and in association with high PCB levels. In a recent study in Flanders including 1600 adolescents enhanced genital development and pubic hair growth has been observed in boys in relation to levels of p,p′-DDE and PCBs in serum (unpublished results). In the North Carolina Infant Feeding Study, no association of PCB exposure to the self-reported timing of puberty (including age at menarche) among 316 girls and 278 boys was found, although there was a non-significant tendency to early maturation in the girls in the highest prenatal exposure group [24]. Two studies from the Great Lake area, Michigan in USA, found no correlation of PCB exposure to self-reported timing of puberty in 327 girls [28] or 151 girls [23]. Similar results were found in a boy cohort (196 boys) from Faroe Islands, that is, no association of PCB exposure to the timing of puberty [29]. In Yucheng, 55 boys who were accidentally exposed to high PCB and polychlorinated dibenzofuran (PCDF) levels were reported to have shorter penile length than the control boys at the same age, suggesting pubertal delay [30]. In summary, epidemiological studies have not revealed any association of PCB exposure with the timing of puberty in girls, whereas in boys there are two studies suggesting a link to delayed puberty and two studies showing no effect.

Table 2.

Epidemiological studies investigating the relationship between pubertal exposure and pubertal development.

Compound	Study area	Study population	Methods	Main findings	Reference
DDE	Precocious puberty patients (Belgium)	26 immigrant girls and 15 native Belgian girls	Patients study Interviews/physical examination Serum measurements	High levels of plasma DDE in immigrant girls (1.04–1.2 μg/l) compared to Belgian native controls (<0.01 ng/ml)	[20]
PCBs Dioxin measured by CALUX	One rural and two urban villages in Belgium	80 boys and 120 girls (17–18 years old) Mean serum PCB levels: 190 (girls) and 360 (boys) pmol/g fat Mean serum CALUX levels: 29 (girls) and 35 (boys) pg Teq/g fat	Cross sectional study Physical examination Pubertal serum levels	Retarded pubertal development associated with higher PCB exposure in boys Retarded breast development associated with higher dioxin levels in girls	[27]
Dioxins	Seweso	282 girls exposed pre-pubertal	Archived serum levels from time of the accident and extrapolated to age at menarche	No effect on age at menarche	[33]
Lead	NHANESIII cross sectional study	2186 girls	Cross sectional study Physical examination Blood lead levels	Delayed pubertal development (breast and pubic hair stage), delayed age at menarche associated with bloodlead >3 μg/dL	[34]
Lead	NHANESIII cross sectional study	1235 girls (0.7–21.7 μg/dl blood lead)	Cross sectional study Physical examination Blood lead levels	Delayed attainment of menarche and pubic hair growth	[35]
Endosulfan	Indian village with high levels of endosulfan used as pesticide	117 boys with serum endosulfan levels of 7.6 ng/g/90 controls with serum levels of 1.4 ng/g	Cross sectional study Physical examination Serum levels	Delayed sexual maturation (tanner stages)	[36]
Phthalates	Puerto Rico	41 patients with premature breast development/35 controls	Case control study Physical examination Serum analysis	Higher levels of DEHP (average of 450 ng/ml) and MEHP (average of 3 ng/ml) in serum of patients (p.p.b. range)	[39]

CALUX, chemically activated luciferase expression; DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; DEHP, di(2-ethylhexyl)phthalate; MEHP, mono-(2-ethylhexyl)phthalate; PCB, polychlorinated biphenyl.

Dioxins act through the aryl hydrocarbon receptor (AhR) and have anti-oestrogenic effects *in vitro* [31]. Oestrogenic effects, however, have been reported as well through interaction of the dioxin–AhR–nuclear translocator complex with oestrogen receptors [32]. A retrospective study of girls exposed to dioxins in Seveso in 1976 found no association with age at menarche [33]. In a Belgian study of children from rural and two urban areas, dioxin exposure was estimated with the chemically activated luciferase expression (CALUX) assay that measures the total dioxin-like activity in serum. There was no correlation of the activity with the age at menarche or pubic hair development, but high exposure was associated with a delay in breast development. In boys, there was no correlation of dioxin-like activity with pubertal development [26,27].

More than 4000 individuals were accidentally exposed to polybrominated biphenyls (PBBs) through the food chain in Michigan in 1973. In a follow-up study of 327 girls, an earlier age at menarche and earlier pubic hair development were reported in girls that had been exposed to high PBB levels *in utero* and by breastfeeding than those who were less exposed and received no breastfeeding. No differences were found in breast development [28].

High lead levels in blood were associated with a delayed age at menarche and delayed pubic hair development in two studies that were based on the National Health and Nutrition Examination Survey in the USA (NHANES III) [34,35]. Breast development was also found to be delayed in the study including 2186 girls [35].

Some newer less-persistent compounds also have hormonal activity. Only a few studies have addressed a possible link between exposure to these compounds and puberty development.

Endosulfan exhibits oestrogenic activity *in vitro* and reduces plasma FSH, LH and testosterone in rats [36,37]. Pubertal delay was associated to a high endosulfan exposure in a recent Indian study where 117 boys from a highly contaminated area were compared to 90 matched control boys from an uncontaminated area [38].

A Puerto Rican epidemy of thelarche has prompted studies on several putative endocrine disrupters, including phthalates

[39]. Furthermore, in a case-control study of 41 girls with thelarche and 35 controls, two-thirds of the cases had measurable phthalate levels in serum, whereas only 14% of the controls had detectable phthalates. However, the phthalate profile in serum raised a concern about possible technical errors (or contamination), because diethylhexyl phthalate concentrations were high as compared to other phthalates [40].

Despite the long-time lapse between birth and puberty onset, three out of six studies reported in table 1 have shown an influence of perinatal exposure on timing of pubertal development. In addition, pubertal exposure has been associated with changes in pubertal development. The existing data do not allow a clear identification of the sensitive time window(s) because the persistent compounds that are studied are already present at the beginning of life and exposure continues throughout life. Follow-up studies including serial serum measurements at time of birth and at pubertal development would be helpful. Another limitation inherent to the epidemiological studies is that human beings are not exposed exclusively to the chemical being investigated, but instead to a mixture of chemicals, some of them acting through common pathways. In addition, no single compound can act as a surrogate or marker for the others, because the contaminant profile varies among individuals.

Compared to girls, the number of studies studying the effect of endocrine disrupters on pubertal development in boys is much more limited. Research in boys is more focused on semen quality, which is much more closely related to fertility.

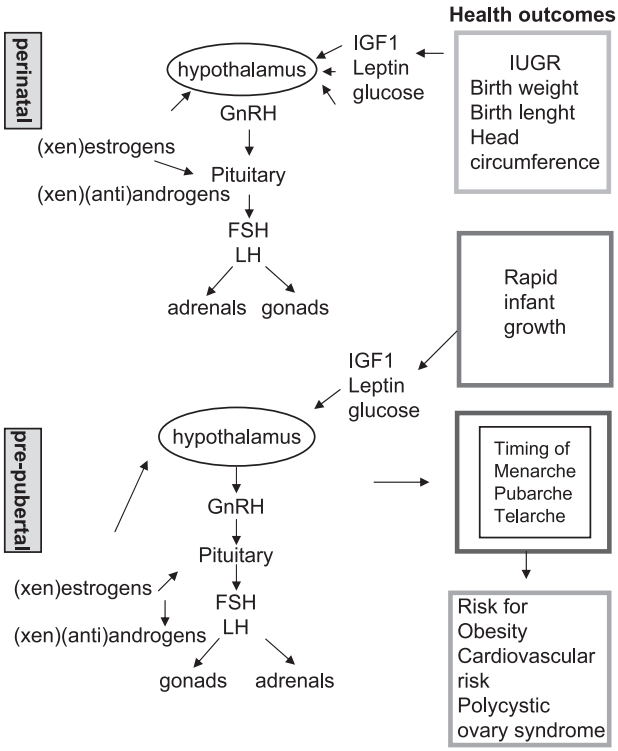

Fig. 1. Schematic illustration of perinatal and postnatal targets for endocrine-disrupting chemicals (EDC) in relation to possible health outcomes.

Animal experiments and mode of action

Animal models have been developed to test the potency of single compounds to evoke changes in pubertal development. Vaginal opening in the female rodent is the initial sign of the oestrogenic rise that accompanies the onset of puberty and first ovulation, also disturbances of oestrus cycle and changes in uterus weight mark pubertal events in rodents [41]. Exposure with endocrine-disrupting chemicals may start *in utero* or after birth, allowing to distinguish the relative importance of prenatal versus postnatal exposure. Advancement in the age at vaginal opening was reported after prenatal exposure to oestradiol, diethylstilboestrol, coumestrol, bisphenol A, octylphenol, nonylphenol, butyl benzyl phthalate, dibutyl phthalate and after exposure with genistein shortly after birth [19]. For some endocrine-disrupting chemicals such as lindane and genistein exposure during gestation accounted for some delay [42]. Irregular oestrus cycles and increases in uterine weight, the latter which is known to be a marker of oestrogenicity, were also commonly observed after exposure to endocrine-disrupting chemicals [19].

In rodents, central programming of sexual maturation takes place between the last week before birth and the first postnatal week [43]. At early exposure times during foetal life and/or the suckling period, an effect on priming of the hypothalamus pituitary axis (HP) was suggested in some rat studies as shown by changes in serum levels of the pituitary hormones FSH and LH. As an example, after exposure to diethylstilboestrol, FSH and LH levels were reduced [44]. Laboratory rodents exposed perinatally to bisphenol A had lower plasma LH concentrations than control animals after long-term ovariectomy [45]. After 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure of immature female rats, both inhibitory and stimulatory responses were observed on the HP axis, as shown by decreases and increases of peak serum levels of FSH and LH [46]. These interferences of endocrine-disrupting chemicals with the HP axis may be due to stimulation of hypothalamic neuronal or pituitary gland cells.

Endocrine-disrupting chemicals may exert both indirect and direct effects on hypothalamic GnRH secreting neurons as oestrogen receptors are present in neurons that project to GnRH neurons, and have been localized within GnRH neurons themselves [47] (fig. 1). *In vivo* and *in vitro* studies have shown oestrogen receptors and androgen receptors in the immature brain. Preliminary observations [19] indicate that o,p′-dichlorodiphenyltrichloroethane could have stimulatory effects on GnRH secretion with involvement of oestrogen receptors and the glutamate receptor as well as the orphan dioxin receptor [32]. Two PCB mixtures, Aroclor 1221 (A1221) and A1254, have been shown to influence GnRH transcript and peptide levels after exposure of the hypothalamic neuronal GT1–7 cells *in vitro* [48].

Alternatively, some compounds such as DDT are known to interfere with brain aromatase, which converts testosterone into oestrogen in the immature brain [49]. The conversion of testosterone to oestradiol plays an important role in the sexual differentiation of the rodent brain [50]. Endocrine-disrupting chemicals may also affect circulating levels of steroids by interfering with steroid production by gonads or with steroid metabolism or with their transporters or their receptors. In immature rats, increased levels of oestrogen activity may suppress GnRH and the pituitary gonadotrophins by a negative feedback control mechanism [51]. In the mature female, a positive (stimulating) feedback may lead to an increase in the preovulatory GnRH and gonadotrophin (FSH and LH) release [3,52] and may enhance puberty onset (fig. 1). The animal data tend to substantiate the effects of endocrine-disrupting chemicals on the hypothalamo–pituitary–gonadal axis that influence sexual maturation and reproduction in female rodents. Direct and indirect effects through feedback mechanisms on hypothalamic and pituitary secreting functions are observed. Furthermore, direct effects on gonadal and adrenal function may contribute to changes in puberty development (fig. 1). The impact on puberty onset may be different according to the timing of exposure.

Prenatal imprinting

As mentioned above, animal studies have suggested that exposure to endocrine-disrupting chemicals *in utero* and in early postnatal stage may influence puberty onset and development. In addition, in human beings there is growing evidence to suggest that the prenatal and early postnatal period may represent an early window of susceptibility to long-term 'programming' of various reproductive outcomes including puberty development. In girls bornSGA, pubertal onset and age at menarche often are advanced, especially if there has been an extensive catch-up growth during the first months of life [53]. In boys born SGA, pubertal timing is reported normal but adult height and testicular volume may be below target [54]. In the UK, MRC 1946 birth cohort, earlier puberty was related to smaller size at birth and rapid growth between 0 and 2 years. Rapid early weight-gain led to taller childhood stature and higher insulin-like growth factor I (IGF-I) levels, possibly through early induction of growth hormone (GH) receptor numbers, and such children were also at risk of childhood obesity [55]. In the Avon Longitudinal Study of Parents and Children, rapid infancy weight-gain was associated with increased risk of obesity at 5 and 8 years, with evidence of insulin resistance, exaggerated adrenarche and reduced levels of sex hormone binding globulin (SHBG) [55]. The role of fat-derived signals, such as leptin, or body size-linked signals, such as IGF-I, or other factors related to energy availability, such as glucose, for timing of puberty and regulation of reproduction is not clear. Data from feed-restricted rats support the notion that leptin could serve as a link between nutritional status and the reproductive axis, and in this way participate in the timing of puberty. The brain might initiate puberty in response to adequate leptin signalling from the periphery [56]. *In vitro* studies have shown that both insulin and leptin that are metabolic factors signalling the nutritional status can trigger hypothalamic neuronal cells and stimulate the expression and secretion of GnRH [57]. Leptin controls also the expression of kisspeptins, which are potent stimulators of hypothalamic GnRH secretion [58]. Enhanced expression of KiSS-1 and their G protein-coupled receptor GPR54 genes, as well as increased GPR54 signalling, are detected at the hypothalamus during pubertal development. Activation of GPR54 by administration of kisspeptin is sufficient to induce precocious activation of the gonadotropic axis in immature rodents and monkeys. Moreover, kisspeptin-expressing neurons are direct targets for the negative and positive feedback actions of sex steroids. Hypothalamic KiSS-1 seems to function as an integrator for peripheral inputs, including gonadal steroids and nutritional signals, controlling gonadotropin-releasing hormone and gonadotropin secretion [59]. Another candidate messenger between nutritional status/energy balance and the hypothalamus is ghrelin [57], which is also capable of stimulation of pulsatile GnRH secretion from prepubertal rat hypothalamic explants. It is now accepted that different metabolic signals, including glucose, insulin and leptin, are capable of modulating reproductive axis activity under specific circumstances, but their exact physiological role remains unknown.

Evidence is also growing that exposure to endocrine-disrupting chemicals may also lead to intra uterine growth retardation and hence may relate to late health effects such as changes in puberty development [60]. In male infants, higher total *in utero* PCB exposure was associated with reduced birth weight, smaller head circumference and reduced weight-for-gestational age. In girls, smaller head circumference and shorter gestations were observed. Prenatal PCB levels were further associated with greater growth in 5-year-old girls, but no apparent effect in 5-year-old boys [61]. Experimental studies have shown a negative effect of developmental PCB exposure on postnatal growth in primates [62] and rodents [63]. The pathways by which xenooestrogens induce intra uterine growth retardation are not fully elucidated. Their interference with steroid and thyroid regulatory mechanisms may play a role. Also direct interference of the steroid activity with lipid metabolism or through induction of liver metabolizing enzymes and pathways may trigger metabolic signals that may act upon the HP axis. It is not yet clear whether these changes in prenatal and early postnatal growth and changes in puberty onset are related in a causal way or are independent targets that are triggered by the same factors.

Conclusion

Puberty marks a transition between childhood and the adult reproductive stage. It is a vulnerable stage of life and deregulation has been linked to increased health and psychosocial problems. Puberty development is a multifaceted process that is under control of different hormonal regulatory

mechanisms. The exact triggers are not yet elucidated. Epidemiological and animal experiments provide evidence for a role of pre-pubertal changes in hormonal control mechanisms but also for early perinatal programming windows. Evidence is accumulating that exogenous hormone disruptors may advance or sometimes delay puberty.

Associations are found between birth outcome, postnatal growth and puberty development, but the causal links are far from understood. Experimental work suggests that exogenous chemicals interfering with targets related to growth, lipid metabolism, differentiation and functioning of brain, gonads and adrenals may play a role. Carefully designed epidemiological studies using exposure markers to endocrine-disrupting chemicals around and/or after birth and in the pre-pubertal stage in combination with markers for endocrine and metabolic status are needed to disentangle eventual causal pathways in environmental settings. We should also be aware that it is not the exposure to an individual chemical, but the cumulative exposure to multiple xenohormones that will define the final impact. Monitoring changes in puberty development should be seen as a sentinel for the impact of environmental changes on developmental and sexual health.

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