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Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides

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In a retrospective auxological study of 145 patients seen in Belgium during a 9-year period for treatment of precocious puberty, 28% appeared to be foreign children (39 girls, one boy) who immigrated 4 to 5 years earlier from 22 developing countries, without any link to a particular ethnic or country background. The patients were either adopted ($n = 28$) or non-adopted ($n = 12$), the latter having normal weight and height at immigration and starting early puberty without evidence of earlier deprivation. This led to the hypothesis that the mechanism of precocious puberty might involve previous exposure to oestrogenic endocrine disrupters. A toxicological plasma screening for eight pesticides detected p,p′-DDE, which is derived from the organochlorine pesticide DDT. Median p,p′-DDE concentrations were respectively 1.20 and 1.04 ng/ml in foreign adopted ($n = 15$) and non-adopted ($n = 11$) girls with precocious puberty, while 13 out of 15 Belgian native girls with idiopathic or organic precocious puberty showed undetectable concentrations (<0.1 ng/ml). A possible relationship between transient exposure to endocrine disrupters and sexual precocity is suggested, and deserves further studies in immigrant children with non-advanced puberty.

Key words: adopted children/organochlorine pesticides/p,p′-DDE/precocious puberty

Introduction

Early puberty in children adopted from developing countries was originally reported in Sweden through a cohort study of 107 Indian girls who had a mean menarcheal age of 11.6 years (Proos *et al.*, 1991). In this cohort of 107 girls, 14 (13%) had menarche before 10 years, consistent with abnormally precocious puberty (PP). A similar advance in mean menarcheal age was observed in another cohort study of 446 girls adopted in The Netherlands from four different countries (Oostdijk *et al.*, 1996). Very recently, 13 patients with PP were reported in France together with a cohort study of 99 adopted children including 52 girls, one-quarter of whom showed menarche before the age of 10 years (Baron *et al.*, 2000). Both authors postulated that the genetic potential as well as factors related to the transition from an underprivileged to a privileged environment could account for early maturation. In Italy, a group of 19 adopted Indian girls with PP was also described (Virdis *et al.*, 1998). These and the French authors (Baron *et al.*, 2000) advocated the role of genetic factors as well as the rapid increase in fat mass possibly increasing free sex steroid concentrations, insulin-like growth factor-I (IGF-I) and leptin. This issue was addressed in a different perspective by studying the patients treated for sexual precocity in Belgium, among whom one-quarter were found to be foreign adopted children (Bourguignon *et al.*, 1992). In the same study it was reported that, during a critical period preceding the onset of puberty, the maturation of some neurotransmitters controlling gonadotrophin-releasing hormone (GnRH) secretion in the rat hypothalamus was accelerated by refeeding and catch-up growth in early undernourished rats. More recently, it was reported in abstract form that, in several adopted children with PP, body mass index (BMI) was normal on arrival in Belgium (Krstevska-Konstantinova *et al.*, 1998) and that several foreign non-adopted patients moving to Belgium with their families presented PP without any evidence of former deprivation (Krstevska-Konstantinova *et al.*, 1999). These observations did not support the hypothesis of recovery from deprivation

as a cause of PP, and led to the postulation of the role of environmental factors changing with immigration. The aim of this study was to evaluate in detail the epidemiological and auxological data of foreign children seen with PP in Belgium. In addition, preliminary toxicological data were obtained with plasma organochlorine pesticide measurements in patients with different aetiologies of PP.

Materials and methods

Patients

This study was conducted in children with PP, with the collaboration of seven Belgian academic paediatric endocrinology units. During the entire study period (1989–2000), the participating physicians met on a monthly basis and discussed all PP patient candidates for GnRH agonist therapy according to the following criteria: breast stage B2 before 8 years of age in girls, and genital stage G2 before 9 years in boys (Tanner, 1962); pubertal response of the gonadotrophins to a standard GnRH test; cerebral imaging (computed tomography or magnetic resonance). The aetiologies of organic PP in the girls was tumoral in 19 (six hamartoma, five suprasellar arachnoidal cyst, three astrocytoma, two choroid plexus papilloma, one third ventricular cyst and two unspecified), post meningitis in three, malformative in four, and microcephaly in one girl. In the foreign patients with PP, the country of origin and the age at immigration were recorded. By comparison, the distribution of the countries of origin among children adopted in Belgium for the period 1991–1997 was obtained from the State Registry (French and Flemish Communities of Belgium) which was established in the early 1990s. In the patients, the early data were obtained from adoption certificates given to foster parents and first medical examination records within the month following arrival. All children had fairly reliable or certain birth dates. Children with peripheral PP (gonadotrophin-independent) or central PP (gonadotrophin-dependent) secondary to peripheral PP were not included in the study. Among the female patients, four girls were excluded due to previous human growth hormone (HGH) therapy and two due to short treatment period and compliance failure. All patients were treated with an intramuscular injection of triptorelin (Depot-Decapeptyl®; IPSEN, Ghent, Belgium) at a dose of 3.75 mg every 4 weeks.

Height was measured using a Harpenden or wall-mounted stadiometer. Height was calculated as Standard Deviation Scores (SDS) (Tanner *et al*., 1966). Weight was measured and expressed as BMI SDS calculated according to a published method (Rolland-Cachera *et al*., 1982). Data on auxology and pubertal development were obtained at 6-month intervals during therapy.

Investigations

Two studies were performed. In a retrospective epidemiological and auxological study, the aetiology of PP and country of origin of patients as well as data (age, height SDS and BMI SDS) at immigration and at diagnosis of PP were evaluated in a group of 145 patients seen in a 9-year period. In a toxicological study, the blood samples obtained in 41 patients on the occasion of a routine follow-up visit were used with the informed consent of the family to measure pesticides including p,p′-DDE [(1,1-dichloro-2,2-bis(4-chlorophenyl) ethylene)], a main metabolite of the insecticide DDT [1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane].

The serum concentration of p,p′-DDE was measured using a gas chromatographic analyser coupled to a Tandem mass spectrometer detector. Seven other pesticides were also measured: DDT, lindane arachlor, heptachlor, aldrin, endrin and hexachlorobenzene (HCB). Sample preparation included a liquid–liquid extraction (petroleum ether:diethyl ether; 98:2) followed by a solid-phase extraction (Bond Elut Certify; Varian, Walnut Creek, CA, USA). The eluate was evaporated to dryness and reconstituted with the derivatization mixture (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA)/trimethylchlorosilane (TMCS) 10% in n-hexane) and then injected into the gas chromatograph (Saturn 2000; Varian). The column was a HP-5 Trace (30 m×0.25 mm internal diameter) from Hewlett Packard (Wilmington, Delaware, USA). Ionization by electronic impact occurred at 70 eV. All solvents were pesticide-grade quality. Reference standards were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). The calibration curve was constructed from 0 to 40 ppb, and linearity applied for this concentration range. Endosulphan-d4 (0.5 ppb) was used as internal standard. The recovery of p,p′-DDE was 96%. The limit of detection (0.1 ppb) was defined as three times the standard deviation (SD) of the results from the lowest quality-control serum pool over the course of the analyses ($n = 15$). For p,p′-DDE, this was consistent with a detection limit of 0.1 ng/ml serum. The coefficients of variation were between 4.6 and 7.8%

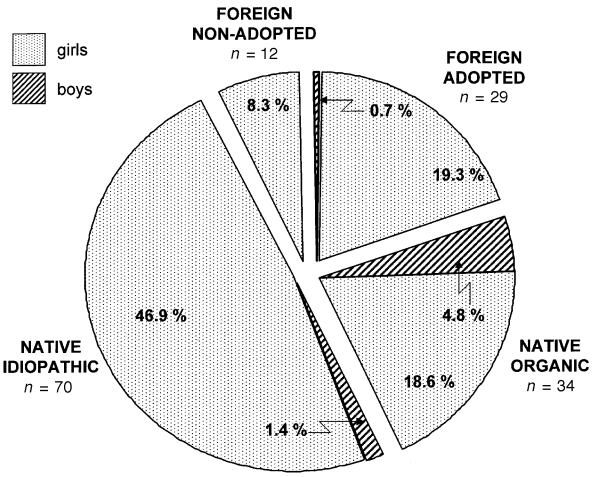

Figure 1. Distribution of the aetiologies of sexual precocity and gender in a retrospective study of 145 patients seen in the Belgian Study Group for Pediatric Endocrinology (BSGPE) and started on treatment using gonadotrophin-releasing hormone (GnRH) agonist (Decapeptyl®).

Data analysis

Results were expressed as mean ± SD. For the serum concentrations of p,p′-DDE, the median concentration was calculated after log transformation of the data. The comparison of mean height and BMI SDS between the patient groups was made using the unpaired Student's *t*-test. The comparison of p,p′-DDE concentrations was made using one-way analysis of variance (ANOVA). All results were considered to be significant at the 5% critical level ($P < 0.05$).

Results

Epidemiological and auxological study

The distribution of the different aetiologies of PP (Figure 1) shows that all conditions occurred much more frequently in girls than in boys. Among 145 patients, 34 had organic PP, while the absence of an observable central nervous system (CNS) cause was consistent with idiopathic forms of PP in the other patients. Only 70 patients with idiopathic PP appeared to be Belgian natives, whereas 41 were immigrants—most of them ($n = 29$) adopted from developing countries. All foreign

Table I. Country of origin of foreign girls with GnRH agonist-treated precocious puberty in Belgium and comparison with the State Adoption Registry (French and Flemish Communities of Belgium)

	Adopted (*n*)		Adopted (*n*)	Non-adopted (*n*)	
	Auxology (1989–1997)	Toxicology (1999–2000)	State Registry[a] (1991–1997)	Auxology (1989–1997)	Toxicology (1999–2000)
Latin America					
Guatemala	2	–	–	–	–
El Salvador	1	–	–	–	–
Columbia	4	2	255	–	–
Nicaragua	1	–	–	–	–
Haïti	–	5	164	–	–
Chile	–	–	40	1	–
Cap Verde	–	–	2	–	1
Ecuador	–	–	57	–	–
Others	–	–	29	–	–
Africa					
Angola	1	–	–	1	1
Rwanda	1	–	126	1	1
Burundi	1	1	101	1	–
Congo	2	1	54	2	2
Benin	–	–	–	1	–
Ivory Coast	1	–	6	–	–
Madagascar	1	–	162	–	–
Nigeria	–	–	–	1	1
Morocco	–	–	6	1	1
Kenya	–	–	–	1	–
Togo	–	–	–	1	1
Ethiopia	–	–	148	–	–
Asia					
India	8	2	637	–	–
Sri Lanka	2	1	14	–	–
Vietnam	1	1	267	–	–
Korea	1	–	–	–	–
Thailand	–	1	95	–	–
Pakistan	–	–	–	1	–
Hong-Kong	–	–	–	–	1
China	–	–	120	–	–
Philippines	–	–	103	–	–
Eastern Europe					
Romania	1	1	88	–	–
Czech. Republic	–	–	–	–	1
Yugoslavia	–	–	–	–	1
Poland	–	–	73	–	–
Russia	–	–	57	–	–
Others	–	–	52	–	–
Total	28	15	2653	12	11

[a]The State Registry database includes children of both sexes.

children had idiopathic PP without evidence of organic aetiology at CNS imaging. There were numerous countries of origin, involving mainly Latin America, Africa and Asia (Table I). Accordingly, the occurrence of PP could not be related to a particular ethnic background. The country distribution of PP patients was consistent with the country distribution in the State Adoption Registry (Table I) except for some countries such as China and Ethiopia. The non-adopted foreign children came partly from countries similar to the adopted group (Table I). Based on a live birth rate in Belgium which is ~100 000 per year, it was calculated that the Belgian native patients with idiopathic PP represented 0.01% of the cumulated children population in a 9-year period, while the foreign adopted patients with PP represented 0.8% of the cumulated group of children adopted in a similar 9-year period.

The patients from the adopted and non-adopted groups showed similar mean ages at immigration (3.9 and 3.3 years respectively) as well as at diagnosis of PP (7.8 and 8.3 years) which was made after an average 4- to 5-year period of living in Belgium (Figure 2A). Using Western European references, the mean height SDS of the foreign children at immigration (Figure 2B) was retarded and shorter (but not significantly so) in the adopted group (–1.4) than in the non-adopted group (–0.7). However, this difference became significant at diagnosis of PP (+0.7 versus +2.3 respectively; $P < 0.05$), after a period of linear growth acceleration. At immigration, weight for height was appropriate in the adopted group, as indicated by a mean BMI SDS close to zero (Figure 2C). In the non-adopted patients, mean BMI SDS at immigration was greater, but not significantly so. At diagnosis, some increase in BMI

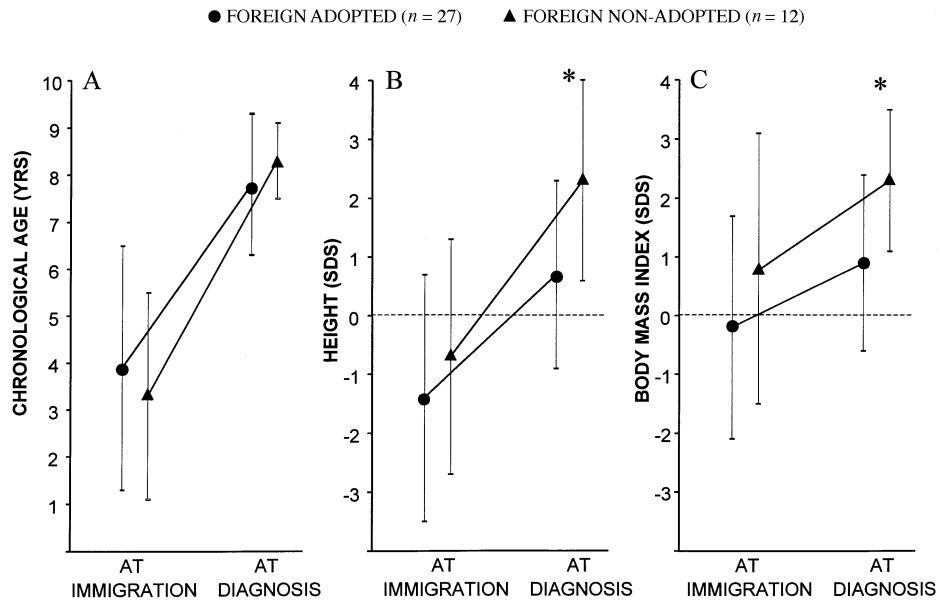

Figure 2. Mean (± SD) data obtained at immigration and at diagnosis of sexual precocity in two groups of foreign children immigrating from developing countries to Belgium for adoption or with their original family (non-adopted). The data are chronological age (**A**), height SDS (**B**) and body mass index SDS (**C**). *$P < 0.05$, adopted versus non-adopted.

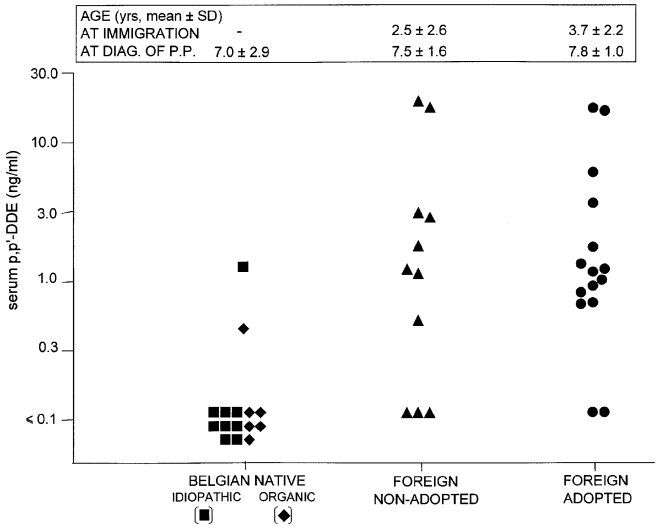

Figure 3. Individual values of serum p,p′-DDE concentrations (log scale) in a cross-sectional study of 15 Belgian native patients with idiopathic or organic PP, 11 foreign non-adopted patients and 15 foreign adopted patients with PP. In both groups of foreign children, the data are significantly higher than in Belgian native patients ($P < 0.001$).

SDS had occurred in both groups, and the mean became greater in the non-adopted patients than in the adopted patients (+2.3 versus +0.9 respectively; $P < 0.01$).

Toxicological study

The foreign children with PP in whom serum concentrations of pesticides were measured came from the same countries as the children studied retrospectively (Table I). Age at immigration and at diagnosis of PP was also similar in the auxological study (Figure 2A) and toxicological study (Figure 3). Except for p,p′-DDE, all the studied pesticides were undetectable. Serum p,p′-DDE concentrations were undetectable in 13 out of 15 Belgian native patients with organic or idiopathic PP (Figure 3). In contrast, only five out of 26 foreign children with PP had undetectable p,p′-DDE concentrations. The median concentration was similar in the foreign adopted patients (1.2 ng/ml) and non-adopted patients (1.04 ng/ml), both groups being significantly higher ($P < 0.001$) than the Belgian natives (0.13 ng/ml). In one girl showing a high p,p′-DDE serum concentration (14.7 ng/ml), DDT was also measurable (0.8 ng/ml).

Discussion

In this study, it was confirmed that precocious puberty occurs in a highly significant proportion of foreign children moving from developing countries to Belgium. Based on the total number of adopted children reported to the Adoption Registry of the French and Flemish Communities of Belgium, the prevalence of PP was found to be 80-fold higher in foreign children than in Belgian natives. This figure however might be overestimated, since some foreign adoption occurred without involvement of the official national organization. The Swedish and Dutch studies showed that the foreign adopted girls, as a group, had early menarche (Proos *et al.*, 1991; Oostdijk *et al.*, 1996). Thus, the present patients are likely to result from a switch towards childhood of the overall distribution of age at onset of puberty instead of a particular subset of fast maturers. This concept is consistent with an increased proportion of borderline advanced puberty in the cohort studies (Proos *et al.*, 1991; Baron *et al.*, 2000). A striking female preponderance of sexual precocity was found in the immigrant children with sexual precocity such as described in the classical idiopathic and organic forms of central PP (Bridges *et al.*, 1994; Grumbach and Styne, 1998). Such sexual dimorphism might result from a final pathophysiological mechanism common to the different forms of central PP and independent of the primary cause. In

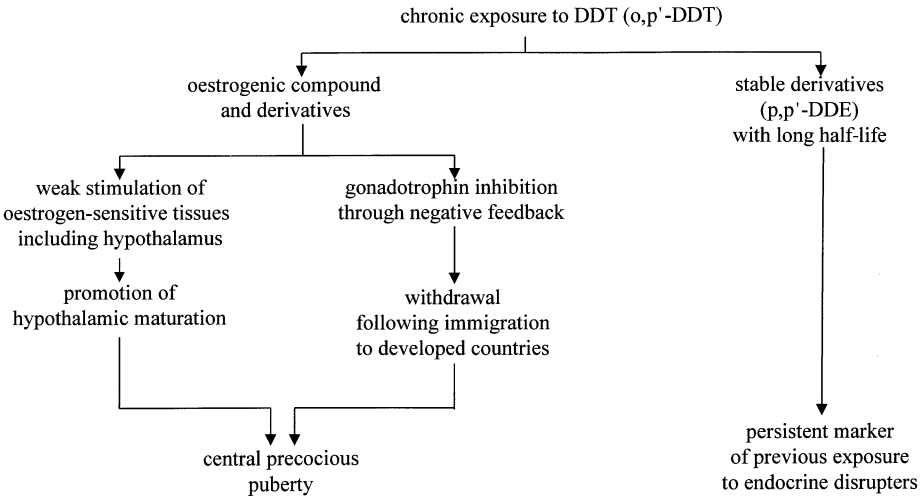

Figure 4. Hypothetical mechanism of organochlorine pesticide involvement as endocrine disruptors in sexual precocity.

addition, the comparison of endocrine disrupter effects between boys and girls may be hampered by the complexity of their mixed oestrogen-like, anti-oestrogen and anti-androgen action (Guillette, 2000).

Observations made in the present study involving many different countries worldwide do not support the concept that a particular ethnic group is at increased risk of PP due to genetic factors. Though Afro-American girls have relatively early menarche (1 year before the white Americans; Herman-Giddens *et al.*, 1997), the African girls have normal or late menarche depending on the nutritional conditions (Burgess and Burgess, 1964), such as in the Indian girls (Proos *et al.*, 1991). It is therefore unlikely that the present findings result from genetic factors linked to the ethnic origin, though their role cannot be excluded.

Many children adopted from developing countries have delayed growth and development due to unfavourable effects of malnutrition and infectious diseases (Miller *et al.*, 1995; Albers *et al.*, 1997; Rutter, 1998). The growth consequences of deprivation were obvious in the Swedish study reporting a mean height SDS of –2.8 in Indian girls on arrival in Sweden. Rapid catch-up growth in the foster country resulted in a recovery of 2 SD in height before the onset of pubertal growth (Proos *et al.*, 1993). In the present study, as in the Italian and French reports (Virdis *et al.*, 1998; Baron *et al.*, 2000), the adopted children showed less retarded growth, though mean age at immigration was not different from the Swedish experience with Indian girls. In addition, some patients entered PP without any evidence of former deprivation. Height and BMI status were often normal at immigration, though national standards from the country of origin were not available. In this study, the existence of PP was highlighted in foreign children moving to Belgium with their original families without history of psychosocial deprivation. It is possible that patients with PP commonly classified as idiopathic in other studies belong to this particular group. On arrival, these children were not height-retarded and some showed obvious weight excess.

Because PP occurred in children moving from developing countries to Belgium irrespective of the ethnic or country background and independent of the height and weight status and the context of adoption, the possible role of environmental factors was pointed out. In developed countries, pubertal signs were observed following increased exposure to xeno-oestrogens such as plastics or insecticides (Marshall, 1993). The present study was focused on the organochlorine pesticide DDT and its derivative p,p′-DDE for several reasons: (i) Among eight organochlorines which were sought in serum from foreign adopted children in a pilot study, p,p′-DDE appeared to be present in several samples while no other compounds were detected; (ii) Some DDT isomers such as o,p'-DDT, o,p'-DDE and p,p'-DDT were shown to exhibit weak but obvious oestrogenic activity in many systems such as the rat uterus (Bitman *et al.*, 1968; Gellert *et al.*, 1972; Bustos *et al.*, 1988), the seagull embryo (Fry and Toone, 1981), the MCF-7 breast cancer cell line (Soto *et al.*, 1992), transfected human embryonal kidney cells or yeast expressing the oestrogen receptor (Kuiper *et al.*, 1998; Sheeler *et al.*, 2000) and vitellogenin induction in rainbow trout liver slices (Shilling and Williams, 2000); (iii) The use of DDT has been banned in western European countries and the USA since the 1960s/early 1970s (Key and Reeves, 1994), whereas it is still used extensively and in large amounts in the developing countries; (iv) In the environment, the breakdown and elimination of DDT takes several decades (Calabrese, 1982), making possible an assessment of contamination several years after stopping chronic exposure to this compound; (v) While the o,p'-isomers are not stable and found in only small amounts in nature (Lamont *et al.*, 1970), the p,p'-isomer derivatives such as p,p′-DDE are more stable and can be used as markers of DDT exposure, though p,p′-DDE does not show obvious oestrogenic activity (Gellert *et al.*, 1972) and does not displace 17β-oestradiol from oestrogen receptor (ER) α or ERβ (Kuiper *et al.*, 1998). However, some oestrogenic effect of p,p′-DDE was reported recently in the salamander (Clark *et al.*, 1998), as well as an anti-androgen action (Kelce *et al.*, 1995).

The mean serum concentration of p,p′-DDE was 10-fold higher in foreign children with PP than in Belgian native patients with PP in whom the organochlorine derivative was usually undetectable. Though this expected finding might be incidental, it may also be related to the occurrence of PP.

Obviously, evidence of pesticide effects should require measurements of p,p′-DDE in foreign adopted girls showing no PP. It could also be helpful to elucidate the reason why children from some countries such as China have not presented with PP so far (age at immigration, early feeding habits, etc.). The contribution of intrauterine exposure to pesticides also warrants further study. Among the foreign non-adopted girls with PP, three were born in Belgium but showed detectable concentrations of p,p′-DDE (data not shown), suggesting possible contamination by the mother during intrauterine life or breast-feeding. An intrauterine effect is particularly interesting since there is some experimental and clinical evidence that the timing of onset of puberty can be affected by sex steroids prenatally (Zachmann *et al*., 1986; Wood *et al*., 1991; Plant, 1994).

In Figure 4, a putative mechanism is proposed of organochlorine involvement in the pathogenesis of PP. There are two possible pathways to account for PP following chronic exposure to oestrogenic DDT-related compounds. A weak stimulation of oestrogen-sensitive tissues may occur peripherally, as seen in an epidemic of PP, possibly due to xeno-oestrogens (Saenz de Rodriguez *et al.*, 1985). A stimulation of oestrogen-sensitive tissues may also occur centrally (Klein *et al*., 1994); these authors explained the physiologically earlier onset of puberty in girls than in boys by the maturation-promoting effects of oestrogens in the female, prepubertally. A similar mechanism was advocated to account for central PP following peripheral isosexual precocity (Pasquino *et al.*, 1987; Kukuvitis *et al.*, 1995). Some evidence against a potentiation of central maturation by environmental oestrogens comes from the absence of early sexual maturation in the developing countries. This issue however may not have been addressed carefully enough so far, and nutritional deprivation may be a confounding factor. It is also possible that pesticides contributed to the advancing menarcheal age in industrialized countries, since the menarcheal age has remained unchanged after the ban on pesticides in the 1960s. An alternative or complementary mechanism (Figure 4) may lie in the negative feedback inhibition of the gonadotrophins, which is a well-established central effect of oestrogen in the prepubertal subject (Kulin and Reiter, 1976; Mauras *et al.*, 1991). Immigration to a developed country may then result in removal of the suppressing effect of oestrogens on the gonadotrophins and subsequent expression of accelerated hypothalaemic maturation. Such a mechanism could also explain the occurrence of central PP following treatment of peripheral PP (Pasquino *et al.*, 1987; Kukuvitis *et al.*, 1995). In children remaining chronically exposed to xeno-oestrogens in the developing countries, the central inhibition may last until it is overcome by endogenous developmental activation, resulting in normal or delayed hypothalamic–pituitary maturation. The absence of increased incidence of PP in Western countries while the use of organochlorine pesticides was prohibited in the 1960s could be explained by the progressive suppression of those pesticides, which is different from the acute withdrawal resulting from a move to Belgium.

In summary, this study provides evidence of increased frequency of sexual precocity in children immigrant from developing countries to Belgium. A possible relationship with exposure to DDT is suggested. These data warrant further analysis, integrating the age at immigration, variations in BMI at immigration and the time spent in the foster country before PP occurs, and the p,p′-DDE concentrations measured.

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